Dissertation on

"PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS USING C-REACTIVE PROTEIN AND APACHE II SCORING SYSTEM"

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CERTIFICATE

This is to certify that the dissertation titled **"PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS BY USING C-REACTIVE PROTEIN AND APACHE II SCORING SYSTEM"** is the bonafide original work done by **Dr. R.PRITHIVIRAJ**, post graduate student, Institute of Internal medicine, Madras medical college, Chennai-3, in partial fulfillment of the University Rules and Regulations for the award of MD Branch -1 General Medicine, under our guidance and supervision, during the academic year 2015-2018.

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DECLARATION

I, **Dr. R.PRITHIVIRAJ**, solemnly declare that dissertation titled **"PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS BY USING C-REACTIVE PROTEIN AND APACHE II SCORING SYSTEM"** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during 2017 under the guidance and supervision of my unit chief **Prof. Dr. S. USHA LAKSHMI., M.D., FMMC.,** Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

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ABBREVIATIONS

APACHE	-	Acute Physiology and Chronic Health Evaluation
ARDS	-	Acute respiratory distress syndrome
COPD	-	Chronic Obstructive Pulmonary Disease
CRP	-	C-reactive protein
DIC	-	Disseminated Intravascular Coagulation
DM	-	Diabetes mellitus
ESR	-	Erythrocyte Sedimentation Rate
IL-1	-	Interleukin 1
IL-6	-	Interleukin 6
LDH	-	Lactate Dehydrogenase
MODS	-	Multiple-organ dysfunction syndrome
PCT	-	Procalcitonin
SAPS	-	Simplified Acute Physiology Score
SIRS	-	Systemic inflammatory response syndrome
SOFA	-	Sequential Organ Failure Assessment
TNF alpha	-	Tumor necrosis factor alpha

CONTENTS

Introduction

INTRODUCTION

The word **sepsis** originated from the old Greek word meaning "**putrefaction**". Nowadays, this term is used to describe the host systemic response to infectious stimuli that is characterised by clinical, haemodynamic, biochemical and inflammatory responses[1] . Sepsis is still one of the leading causes of death in the critically ill patients[2].

In daily practice, clinicians are often faced with two dilemmas: 1.whether a patient is infected or not, and 2.whether the antibiotic therapy being given is effective. The distinction between infection and sepsis is frequently difficult to make. Infection without sepsis can occur if the process remains localised. A sepsis-like syndrome without infection is also a frequent finding in conditions such as trauma and pancreatitis[3].

The attention of the clinician must be directed towards the early diagnosis of infection[4] . However, bacteriological confirmation may be difficult to obtain and negative cultures do not exclude the presence of infection. In addition, manifestations of sepsis such as fever, leukocytosis and tachycardia are neither specific nor sensitive for infection, nor for monitoring the response to therapy [5].

Increasing understanding of the various inflammatory cascade mechanisms has given new insights and provided several markers that, in conjunction with other manifestations of sepsis, can be useful as indicators of infection. **C-reactive protein (CRP)** is one such marker.

A marker of sepsis has been defined as "***a measure that identifies a normal biologic state or that predicts the presence or severity of a pathologic process OR DISEASE***."[7]

Many biochemical markers and clinical scoring systems are used to assess the severity and outcome of sepsis. If one prognostic method is used that should be simple, easily available, should have good sensitivity and specificity.

Acute phase reactants are non-specific and elevated in infection, inflammation, trauma and neoplasms. CRP levels are widely used as a relatively non-specific marker of inflammation. Many studies have demonstrated increased CRP levels in patients with sepsis; increasing or persistently high levels suggest a poor prognosis, while declining values are associated with a more favourable prognosis.

In the present study, serum CRP concentrations in all patients admitted to the emergency ward with clinical sepsis were measured and compared their prognostic value in the assessment of severity and mortality.

Aims & objectives

AIMS AND OBJECTIVES

- To study the outcome of patients with sepsis by using both scoring system (APACHE II) and acute phase reactant (CRP).

Review of literature

REVIEW OF LITERATURE

Definitions

Animals mount both local and systemic responses to microbes that traverse their epithelial barriers and enter underlying tissues. Fever or hypothermia, leukocytosis or leukopenia, tachypnea, and tachycardia are the cardinal signs of the systemic response that is often called the ***systemic inflammatory response syndrome*** **(SIRS)**. SIRS may have an infectious or a non-infectious etiology. If infection is suspected or proven, a patient with SIRS is said to have ***sepsis.*** When sepsis is associated with dysfunction of organs distant from the site of infection, the patient has ***severe sepsis***. Severe sepsis may be accompanied by hypotension or evidence of hypoperfusion.

When hypotension cannot be corrected by infusing fluids, the diagnosis is ***septic shock***. Shock occurs when there is a mismatch between the metabolic needs and the arterial flow. Sepsis is the most common cause for the distributive shock and it accounts for nearly 50%. Sepsis and related disorders formal definition were laid by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine(SCCM) consenses conference in 1991.The 1992 statement from the ACCP/SCCM consensus conference introduced into common parlance the term SIRS.

There is evidence that the different stages may form a continuum. After understanding the pathophysiology of sepsis and related conditions better the definition for these were re-visited in 2001 under ACCP, SCCM, European Society of Critical care medicine

Bacteremia - Presence of bacteria in blood, as evidenced by positive blood cultures.

Septicemia - Presence of microbes or their toxins in blood. Its a serious Blood stream infection.it is also known as blood poisoning.it should be treated in the hospital, or else septicaemia can progress to sepsis. Septicemia is caused by an infection in another part of the body.

Systemic inflammatory response syndrome (SIRS)

Two or more of the following conditions:

1. Fever (oral temperature >38°C) or hypothermia (<36°C);
2. Tachypnea (>24 breaths/min);
3. Tachycardia (heart rate >90 beats/min);

4. Leukocytosis (>12,000/microL), leukopenia (<4,000/microL), or >10% bands; may have a non-infectious etiology this SIRS concept was globally accepted by clinicians and investigators.

   SIRS can be trigerred by various infective and non-infective causes. Signs of inflammation occurs in patients without infection also such as in burns, pancreatitis and other conditions too.

The clinical manifestations of SIRS may be not uniform but the biochemical may be more consistant than the clinical features. There may be an elevated levels of IL-6,adrenomedullin,soluble CD 14,soluble endothelial and leucocyte adhesion molecule 1,extra cellular phospholipase A2,CRP.in future we can solely use the biochemical data alone when the epidemiological data supports rather than the clinical criteria.

Sepsis - SIRS that has a proven or suspected microbial etiology. It can be Trigerred by bactria and fungi that usually won't cause the infection in Immunocompetent individuals. It is very important to have the tools needed to recognise and diagnose the sepsis promptly.as in 1992 we define sepsis when SIRS is associated with microbial organisms.

The criteria to identify the sepsis should be useful to both clinicians and the researchers. It should be more sensitive to identify most patients with the syndrome while minimally sacrificing the inevitable specificity.

The laboratory dependent criteria should be use the markers that is widely available today or it should be available widely in the future. The criteria should be useful and fit to all adults, paediatrics and neonatal patients too.

Severe sepsis (similar to "sepsis syndrome")

The definition for the severe sepsis is not changed and it refers to sepsis complicated by organ dysfunction. It is the most common cause of mortality in non-coronary critical care units. More than 200000 people are dying due to this severe sepsis yearly.

Organ dysfunction can be defined by the definition that is developed by the MARSHAL et al. In paediatric population it can be defined by using the definition that is formulated by the WILKINSON et al.

Sepsis with one or more signs of organ dysfunction—for example:

1. *Cardiovascular:* Arterial systolic blood pressure <90 mmHg or mean arterial pressure<70 mmHg that responds to administration of intravenous fluid

2. *Renal:* Urine output <0.5 mL/kg per hour for 1 hour despite adequate fluid resuscitation

3. *Respiratory:* Pa_{O2}/FI_{O2} <=250 or, if the lung is the only dysfunctional organ, <=200

4. *Hematologic:* Platelet count <80,000/microL or 50% decrease in platelet count from highest value recorded over previous 3 days

5. *Unexplained metabolic acidosis:* A pH <=7.30 or a base deficit >=5.0 mEq/L and a plasma lactate level >1.5 times upper limit of normal for reporting lab

6. *Adequate fluid resuscitation:* Pulmonary artery wedge pressure >=12 mmHg or central venous pressure >=8 mmHg

Septic shock

Sepsis with hypotension (arterial blood pressure <90 mmHg systolic, Mean arterial pressure of less than 60 or 40 mmHg less than patient's normal blood pressure) for at least 1 hour despite adequate fluid resuscitation; Children can maintain the high vascular tone than the adults. So the hypotension can occurs earlier than adults in children and neonates.

Or

Need for vasopressors to maintain systolic blood pressure >=90 mmHg *or* mean arterial pressure >=70 mmHg

Refractory septic shock

Septic shock that lasts for >1 hour and does not respond to fluid or pressure administration.

Multiple-organ dysfunction syndrome (MODS)

Dysfunction of more than one organ, requiring intervention to maintain homeostasis. It is a process rather than a disease. Alteration in organ function can vary widely between mild dysfunction to completely irreversible organ failure.in the classic 1975 editorial by BAUE the concept of multiple progressive or sequential systems failure was formulated. The term MODS was lastly found as a more appropriate term. It is defined as a clinical syndrome characterised by the development of reversible, progressive physiological dysfunction in 2 or more organ systems.

Etiology:

Sepsis can be a response to any class of microorganism. Microbial invasion of the bloodstream is not essential, since local inflammation can also elicit distant organ dysfunction and hypotension. In fact, blood cultures yield bacteria or fungi in only 20–40% of cases of severe sepsis and 40–70% of cases of septic shock. Individual gram-negative or gram-positive bacteria account for 70% of these isolates; the remainder are fungi or a mixture of microorganisms. Falciparum malaria, Dengue and enteric fever may cause the septic shock in India.

Microorganisms	Episodes with Bloodstream Infection, % (*n* = 436)	Episodes with Documented Infection but No Bloodstream Infection, % (*n* = 430)	Total Episodes, % (*n* = 866)
Gram-negative bacteria[a]	35	44	40
Gram-positive bacteria[b]	40	24	31
Fungi	7	5	6
Polymicrobial	11	21	16
Classic pathogens[c]	<5	<5	<5

[a] Enterobacteriaceae, pseudomonads, *Haemophilus* spp., other gram-negative bacteria. [b] *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, *Streptococcus pneumoniae*, other streptococci, other gram-positive bacteria. [c] Such as *Neisseria meningitidis, S. pneumoniae, Haemophilus influenzae*, and *Streptococcus pyogenes.*

Source: Adapted from KE Sands et al: JAMA 278:234, 1997.

Epidemiology

Severe sepsis can cause death in more than 200000 population in unites states. Incidence is increased in the past 30 years that accounts for 3 per 1000 populations. The incidence is increased with the age and underlying disorder. Widespread use of indwelling catheters ,mechanical devices also play a important role.

Invasive bacterial infections are the most common cause of sepsis around the world especially in young children. Non typhoidal salmonella, pneumococcus, H.influenza, E.coli were the most commonly isolated bacterias.

Pathophysiology

The hallmark of sepsis is the mismatch between host and intensity of the pathogenic stimuli that leads to organ dysfunction and injury. Most cases of severe sepsis are triggered by bacteria or fungi that do not ordinarily cause systemic disease in immunocompetent hosts . To survive within the human body, these microbes often exploit deficiencies in host defenses, indwelling catheters or other foreign matter, or obstructed fluid drainage conduits. Microbial pathogens, in contrast, can circumvent innate defenses because they

(1) lack molecules that can be recognized by host receptors or (2) elaborate toxins or other virulence factors. In both cases, the body can mount a vigorous inflammatory reaction that results in severe sepsis yet fails to kill the invaders. The septic response may also be induced by microbial exotoxins that act as superantigens (e.g., toxic shock syndrome toxin) as well as by many pathogenic viruses.

Local and Systemic Host Responses to Invading Microbes

Recognition of microbial molecules by tissue phagocytes triggers the production and/or release of numerous host molecules (cytokines, chemokines, prostanoids, leukotrienes, and others) that increase blood flow to the infected tissue, enhance the permeability of local blood vessels, recruit neutrophils to the site of infection, and elicit pain.

These reactions are familiar elements of local inflammation, the body's frontline innate immune mechanism for eliminating microbial invaders. Systemic responses are activated by neural and/or humoral communication with the hypothalamus and brainstem; these responses enhance local defenses by increasing blood flow to the infected area, augmenting the number of circulating neutrophils, and elevating blood levels of numerous molecules (such as the microbial recognition proteins discussed above) that have anti-infective functions.

Cytokines and Other Mediators

Cytokines can exert endocrine, paracrine, and autocrine effects . TNF-alpha stimulates leukocytes and vascular endothelial cells to release other cytokines to express cell-surface molecules that enhance neutrophil-endothelial adhesion at sites of infection, and to increase prostaglandin and leukotriene production.

Although TNF-alpha is a central mediator, it is only one of many proinflammatory molecules that contribute to innate host defense. Chemokines, most prominently interleukin (IL)-8 and IL-17, attract circulating neutrophils to the infection site. IL-1beta exhibits many of the same activities as TNF-alpha. IFN gamma, IL-12, IL-17, and other proinflammatory cytokines probably interact synergistically with one another and with additional mediators. The nonlinearity and multiplicity of these interactions have made it difficult to interpret the roles played by individual mediators in both tissues and blood.

Coagulation Factors

Intravascular thrombosis, a hallmark of the local inflammatory response, may help wall off invading microbes and prevent infection and inflammation from spreading to other tissues. IL-6 and other mediators promote intravascular coagulation initially by inducing blood monocytes and vascular endothelial cells to express tissue factor. When the tissue factor is exposed it binds to factor VII a that converts the factor IX and X to its active form. It activates both pathways and forms the fibrin thread. The increased plasminogen activator inhibitor 1 levels reduces the protein C and protein S levels that also favours the formation of fibrin thread. The deposition of fibrin is more common in patients with endothelial infection such as meningococcemia. It can sometimes leads to the formation of DIC.

Neutrophilic Extracellular Traps (NET) will produced when the neutrophils are stimulated. It will kill the bacterias and fungi by using the elastase. It also play a role in forming hypoperfusion in sepsis but it yet to be proved.

CONTROL MECHANISMS

1. Local Control Mechanisms

The anti-inflammatory forces that put out the fire and clean up the battleground include molecules that neutralize or inactivate microbial signals. Among these molecules are intracellular factors (e.g., suppressor of cytokine signalling 3 and IL-1 receptor–associated kinase 3) that diminish the production of proinflammatory mediators by neutrophils and macrophages; anti-inflammatory cytokines (IL-10, IL-4); and molecules derived from essential polyunsaturated fatty acids (lipoxins, resolvins, and protectins) that promote tissue restoration.

2. Systemic Control Mechanisms

Systemic responses to infection diminish the cellular responses to microbial molecules. Circulating levels of anti-inflammatory cytokines (e.g., IL-10) increase even in patients with mild infections. Glucocorticoids inhibit cytokine synthesis by monocytes in vitro; the increase in blood cortisol levels early in the systemic response presumably plays a similarly inhibitory role.

Epinephrine inhibits the TNF-alpha response to endotoxin infusion in humans while augmenting and accelerating the release of IL-10; prostaglandin E2 has a similar "reprogramming" effect on the responses of circulating monocytes to LPS and other bacterial agonists. Cortisol, epinephrine, IL-10, and C-reactive protein reduce the ability of neutrophils to attach to vascular endothelium, favouring their demargination and thus contributing to leukocytosis while preventing neutrophil-endothelial adhesion in uninflamed organs.

Studies in rodents found that macrophage cytokine synthesis is inhibited by Ach that is produced by the CD4 cells. There is also evidence suggests that this is immunosuppressant.

IL-6 plays a main role in trigerring the sepsis. It is an important stimulus for hypothalamo-pituitary-adrenal axis is the major procoagulant cytokine too. It is a principle inducer of the acute phase response. Other acute phase reactants are protease inhibitors and antioxidants neutralises the harmful substances that are released from the neutrophils. Due to the sequestration of the iron into the hepatocytes the serum iron levels were reduced.

It can thus be concluded that both local and systemic responses to infectious agents benefit the host in important ways. Most of these responses and the molecules responsible for them have been highly conserved during animal evolution and therefore may be adaptive. Elucidating how they contribute to lethality—i.e., become maladaptive—remains a major challenge for sepsis research.

Organ Dysfunction and Shock

As the body's responses to infection intensify, the mixture of circulating cytokines and other molecules becomes very complex: elevated blood levels of more than 50 molecules have been found in patients with septic shock. Although high concentrations of both pro- and anti-inflammatory molecules are found, the net mediator balance in the plasma of these extremely sick patients seems to be anti-inflammatory.

Endothelial Injury

Many investigators have favoured widespread vascular endothelial injury as the major mechanism for multiorgan dysfunction. Many factors are contributing to the endothelial injury among that leukocyte derived mediators

and platelet-leucocyte-fibrin are the main culprits. The stimuli to produce cytokines from the vascular endothelium is mainly the TNF-alpha.

These cytokines attracts the phagocytes to infected sites and activates their anti microbial arsenals, endothelial cell activation promotes microvascular thrombosis leads to DIC and hypotension and shock.

Luminal obstruction of capillaries due to endothelial cell swallowing leads to tissue hypoxia. Oxydative phosphorylation may also impaired and ATP production too. These too contributes to tissue hypoxia.

Septic Shock

The hallmark of septic shock is a decrease in peripheral vascular resistance that occurs despite increased levels of vasopressor catecholamines. Prominent hypotensive molecules include nitric oxide, beta-endorphin, bradykinin, platelet-activating factor, and prostacyclin.

The pathogenesis of severe sepsis may differ according to the infecting microbe, the ability of the host's innate defense mechanisms to sense it, the site of the primary infection, the presence or absence of immune defects, and the prior physiologic status of the host.

Clinical Manifestations

The manifestations of the septic response are superimposed on the symptoms and signs of the patient's underlying illness and primary infection. The rate at which severe sepsis develops may differ from patient to patient, and there are striking individual variations in presentation.

The initial sign of sepsis is hyperventilation. other manifestations are disorientation, confusion and other manifestations of encephalopathy. focal neurological signs are uncommon in sepsis patients.

Bacterial toxins may spread hematologically and leads to the formation of diffuse cutaneous reactions. When the skin lesions are associated with the sepsis then we can think of a specific etiological agents like N.Meningitidis and H.Influenza.

GIT manifestations also can occur in patients with sepsis such as nausea, vomiting, diarrhoea and ileus. Upper gastro intestinal bleed can occur due to stress ulcers. Cholestatic jaundice and elevated alkaline phosphatase levels can occur in sepsis patients. Prolonged hypotension can leads to acute liver injury and ischemic bowel injury.

Lactate levels will rise due to the formation of excessive lactate levels. Cytokine derived acute phase response will enhance the production of CRP, fibrinogen and complements. Protein catabolism will also increased. Serum albumin will decrease due to decreased hepatic production and movement of albumin into the interstitial space.

Major Complications

1. Cardiopulmonary Complications

Ventilation-perfusion mismatching produces a fall in arterial PO_2 early in the course. Progressive diffuse pulmonary infiltrates and arterial hypoxemia (Pa_{O2}/FI_{O2}, <300) indicate the development of acute lung injury; more severe hypoxemia (Pa_{O2}/FI_{O2}, <200) denotes the **acute respiratory distress syndrome (ARDS).**

Sepsis-induced hypotension (see "Septic Shock," above) usually results initially from a generalized maldistribution of blood flow and blood volume and from hypovolemia that is due, at least in part, to diffuse capillary leakage of intravascular fluid.

Depression of myocardial function, manifested as increased end-diastolic and systolic ventricular volumes with a decreased ejection fraction, develops within 24 hours in most patients with severe sepsis.

2. Renal Complications

Oliguria, azotemia, proteinuria, and non-specific urinary casts are frequently found. Many patients are inappropriately polyuric; hyperglycemia may exacerbate this tendency. Most renal failure is due to acute tubular necrosis induced by hypotension or capillary injury.

3. Coagulopathy

Although thrombocytopenia occurs in 10–30% of patients, the underlying mechanisms are not understood. Platelet counts are usually very low (<50,000/microL) in patients with DIC.

4. Neurologic Complications

When the septic illness lasts for weeks or months, "critical illness" polyneuropathy may prevent weaning from ventilatory support and produce distal motor weakness. Electrophysiological studies are diagnostic. Guillain-Barre syndrome, metabolic disturbances, and toxin activity must be ruled out.

5. Immunosuppression

Patients with severe sepsis are often profoundly immunosuppressed. Manifestations include loss of delayed-type hypersensitivity reactions to common antigens, failure to control the primary infection, and increased risk for secondary infections (e.g., by opportunists such as *Stenotrophomonas maltophilia, Acinetobacter calcoaceticus-baumannii,* and *Candida albicans*)[8]. Increasing understanding of the various inflammatory cascade mechanisms has given new insights and provided several markers that, in conjunction with other manifestations of sepsis, can be useful as indicators of infection. C-reactive protein (CRP) is one such marker.

HOW TO DIAGNOSE SEPSIS

There is no specific diagnostic test for sepsis. The clinical findings in patients with sepsis are fever/hypothermia, tachycardia, tachypnea, respiratory alkalosis and hypotension. We must find the definitive etiological agent for sepsis. Atleast we need 2 blood culture samples for diagnosis from a different locations. Skin and mucosa also should be examined to get a clue or to even diagnose a etiological agent for sepsis.

HOW TO TREAT SEPSIS

Patients should be treated with in 1 hour of diagnosis with sepsis or septic shock.

ANTIMICROBIAL THERAPY

It is proven that starting antibiotics with in 1 hour of receiving the patient is associated with the lowest mortality rates. But the inappropriate antibiotics selection will leads to lower survival rates.

Emperical antimicrobial therapy should be initiated that should cover both gran positive and negative organisms. Maximal recommended dose should be given to the patient in intravenous route. If the patient is febrile more than 5 days of starting antibiotics, neutropenic with long standing indwelling catheters should also started with antifungals too.

Clinical Condition	Antimicrobial Regimens (Intravenous Therapy)
Immunocompetent adult	The many acceptable regimens include (1) piperacillin-tazobactam (3.375 g q4–6h); (2) imipenem-cilastatin (0.5 g q6h), ertapenem (1 g q24h), or meropenem (1 g q8h); or (3) cefepime (2 g q12h). If the patient is allergic to β-lactam agents, use ciprofloxacin (400 mg q12h) or levofloxacin (500–750 mg q12h) plus clindamycin (600 mg q8h). Vancomycin (15 mg/kg q12h) should be added to each of the above regimens.
Neutropenia (<500 neutrophils/μL)	Regimens include (1) imipenem-cilastatin (0.5 g q6h) or meropenem (1 g q8h) or cefepime (2 g q8h) or (2) piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h). Vancomycin (15 mg/kg q12h) should be added if the patient has an indwelling vascular catheter, has received quinolone prophylaxis, or has received intensive chemotherapy that produces mucosal damage; if staphylococci are suspected; if the institution has a high incidence of MRSA infections; or if there is a high prevalence of MRSA isolates in the community. Empirical antifungal therapy with an echinocandin (for caspofungin: a 70-mg loading dose, then 50 mg daily), voriconazole (6 mg/kg q12h for 2 doses, then 3 mg/kg q12h), or a lipid formulation of amphotericin B should be added if the patient is hypotensive, has been receiving broad-spectrum antibacterial drugs, or remains febrile 5 days after initiation of empirical antibacterial therapy.

Splenectomy	Cefotaxime (2 g q6–8h) or ceftriaxone (2 g q12h) should be used. If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin. If the patient is allergic to β-lactam drugs, vancomycin (15 mg/kg q12h) plus either moxifloxacin (400 mg q24h) or levofloxacin (750 mg q24h) should be used.
IV drug user	Vancomycin (15 mg/kg q12h) is essential.
AIDS	Cefepime alone (2 g q8h) or piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h) should be used. If the patient is allergic to β-lactam drugs, ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q12h) plus vancomycin (15 mg/kg q12h) plus tobramycin should be used.

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Source: Adapted in part from DN Gilbert et al: *The Sanford Guide to Antimicrobial Therapy,* 43rd ed, 2013.

REMOVAL OF THE SOURCE

The focus for sepsis should be removed. The occult infective focus also sought carefully. All catheters should be removed and that should be replaced with newer one if the patient needs that.

HEMODYNAMIC SUPPORT

Adequate oxygen perfusion should be maintained in patients with sepsis is very essential. They should be monitored the essential parameters like BP, urine output and skin perfusion. Urine output should be maintained above 0.5ml/hour/kg. Mean arterial pressure should be maintained **above** 65mmhg.If the patient is in shock patient should be started with noradrenaline support.

If the bp is not getting rised despite the inotropic support should strongly suspect the adrenal insufficiency and patient should receives the Hydrocortisone 50 mg every 6^{th} hourly. It should be continued upto 7 days and tapered and stopped.

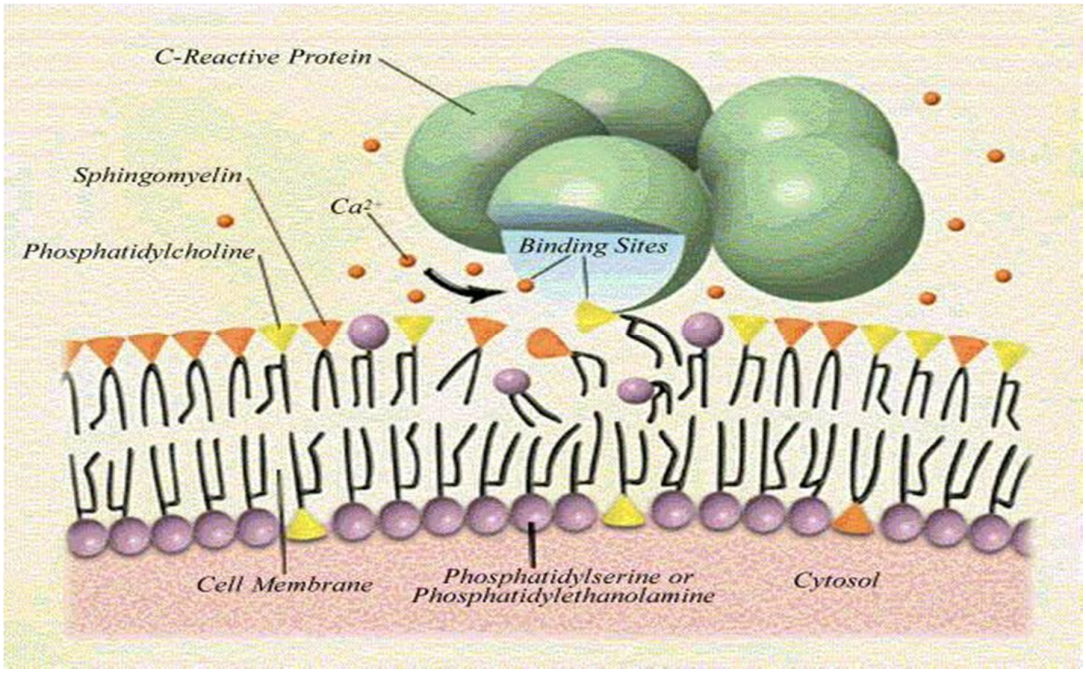
Ventilator therapy can be initiated for progressive hypoxia, hypercapnia, neurological deterioration, impending respiratory failure.

Erythropoietin is generally recommended when the blood HB levels are below 7. Bicarbonate can be given for severe metabolic acidisis (<7.2pH).

C-REACTIVE PROTEIN

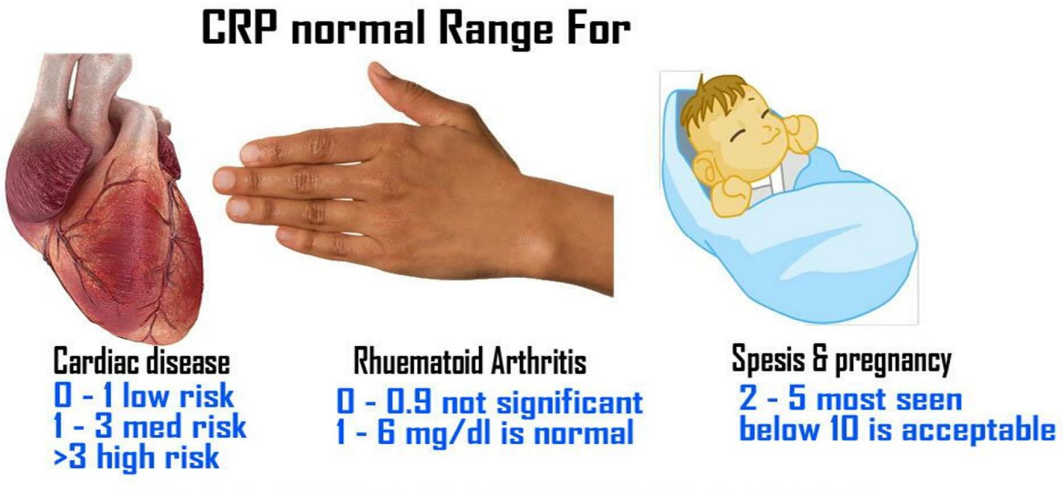
Physiology of C-reactive protein

C-reactive protein is a long-established marker of sepsis. In 1930, Tillet and Francis identified, in the sera of patients with pneumonia, the capacity to precipitate polysaccharide fractions, designated as fraction C, from *Streptococcus pneumoniae*[9]. This property quickly disappeared as patients recovered and was not identified in healthy volunteers. When the cause of this reaction was identified as a protein, it was named CRP. The "acute phase" designation was introduced to classify acutely ill patients with infection whose sera was CRP positive. Since then, several other acute phase proteins have been described.



C-reactive protein belongs to the pentraxin family of proteins, so called because they form a cyclic pentamer composed of five identical non-glycosylated sub-units. C-reactive protein binds to several polysaccharides and peptido-polysaccharides present in bacteria, fungi and parasites in the presence of calcium. These complexes activate the classical complement pathway, acting as opsonins and promoting phagocytosis[10]. Together with complement components, CRP is the only acute phase protein directly involved in the clearance of micro-organisms.

The serum concentration of CRP in the normal human population has a median of 0.8 mg/l (interquartile range 0.3–1.7 mg/l) and is below 10 mg/l in 99% of normal samples[11,12]. Levels above these values are abnormal and indicate the presence of a disease process.



As with many other acute phase proteins, CRP is predominantly synthesised by the liver, mainly in response to interleukin 6 (IL-6) . A good correlation exists between CRP and IL-6 levels [13]. Tumour necrosis factorα (TNFα) and IL-1 are also regulatory mediators of CRP synthesis . The secretion of CRP begins within 4–6 h of the stimulus, doubling every 8 h and peaking at 36–50 h.

Elevations in serum CRP are seen with most invasive infections[14,15]. Both acute systemic Gram-positive and Gram-negative bacterial infections, as well as systemic fungal infections cause marked CRP rises, even in immunodeficient patients. By contrast, CRP concentrations tend to be lower in most acute viral infections. Nevertheless, this rule is not absolute and uncomplicated infections with adenovirus, measles, mumps and influenza are sometimes associated with high CRP levels.

In addition to infection, there are several other conditions that commonly lead to substantial changes in CRP concentrations. These include trauma, surgery, burns, tissue necrosis, immunologically mediated inflammatory diseases, crystal-induced inflammatory diseases and advanced cancer.

CLINICAL APPLICATIONS OF C-REACTIVE PROTEIN

A. Evaluation of a single C-reactive protein determination

1. Sepsis diagnosis

The value of a single CRP measurement in sepsis diagnosis has been investigated in different clinical situations. In two recently published studies in critically ill patients, the best cut-off for the diagnosis of sepsis was 50 mg/l (sensitivity 98.5% and specificity 75%) and 79 mg/l (sensitivity 71.8%, specificity 66.6%) [16,17]

2. Disease severity

The single determinant of CRP level is its rate of synthesis, which in turn depends on the inflammatory insult intensity. In a recent study, CRP levels from each septic patient were grouped according to the ACCP/SCCM Consensus Conference classification . Mean values were 70 mg/l in systemic inflammatory response syndrome (SIRS) patients, 98 mg/l in sepsis, 145 mg/l in severe sepsis and 173 mg/l in septic shock, probably reflecting different degrees of inflammatory response [18].

3. Outcome prediction

Besides its use in the diagnosis of sepsis, CRP has also been evaluated as a prognostic marker. Non-survivors had a median CRP concentration on admission of 70 mg/l, significantly higher than that measured in survivors (18 mg/l)[19]

B. Evaluation of serial c-reactive protein determinations

There is a large body of literature dealing with clinical applications and the discriminative value of a single CRP value. However, it is more important to follow its evolution over the duration of hospital stay. Changes are very helpful in diagnosis as well as in monitoring response to therapy, as CRP levels are only determined by the rate of synthesis.

In contrast, other acute phase phenomena such as leukocytosis and fever are dependent on complex mechanisms involving several mediators. Therefore, these markers are not reliable markers of sepsis.

1. Sepsis diagnosis

Infection should always be suspected if there is a steady increase in CRP levels over 2–3 days in the absence of an intervention likely to mount an inflammatory response.

2. Response to therapy

After the diagnosis of infection and the start of therapy, serial determinations of CRP provide important information. The value of CRP changes over time has not yet been systematically investigated, but in several papers the authors recognised that decreases in CRP levels coincide with clinical improvements while, on the other hand, CRP increases suggest infectious complications.[20,21]

In conclusion, serial CRP measurement, rather than a single determination at the time of admission, is a simple and valuable instrument in the diagnosis of sepsis and infection as well as in monitoring the response to therapy.

Other markers of infection

The classic markers of infection are fever and leukocytosis. Although economical and easy to measure, body temperature is a specific, but not sensitive, marker of infection[22,23]. The WCC count is routinely performed in almost every ICU and is also a criterion of sepsis. It is influenced by many non-infectious factors, such as acute myocardial infarction, catecholamines, corticosteroids and acute bleeding.[24]

PCT (Procalcitonin) was described more recently and is not routinely measured in all hospital laboratories. PCT levels have been shown to correlate with the severity of sepsis as measured by the acute physiology and chronic health evaluation **(APACHE) II** or sequential organ failure assessment **(SOFA)** scores, and a recent meta-analysis reported that PCT was more sensitive and specific than CRP for differentiating bacterial from noninfective causes of inflammation.

In addition, PCT is produced and cleared more rapidly than CRP, making it potentially more useful for identifying infection early and for following the progress of disease. Using a new sensitive and rapid PCT assay, Christ-Crain et al. have shown that PCT-guided therapy can reduce total antibiotic exposure and antibiotic treatment duration in patients with community-acquired pneumonia.

However, further studies are needed to confirm these results and to evaluate the use of PCT levels to guide therapy in heterogeneous groups of patients. Further study is also needed to define and validate specific cut-off values in different disease states.

Clinicians using PCT as a marker of infection should be aware of some important and potentially dangerous limitations. The behaviour of PCT in acute renal failure is still unknown .

In cardiac surgery patients complicated with mediastinitis, PCT concentrations were almost normal (0.8±0.58 ng/ml) incomparison with noninfected patients (0.41±0.36 ng/ml)[25]. In a study in critically ill patients, PCT was below 1.0 ng/ml in 12.5% and 62.5% of infected patients with and without septic shock, respectively[26]. Finally, in community-acquired pneumonia PCT can be normal or even undetectable (median 0.2 ng/ml, range 0.1–6.7 ng/ml, *n*=149) . There is no obvious explanation for these unexpected findings. With regard to cost, measurement of PCT is considerably more expensive than CRP.

Prognostic Scoring Systems

The high-complexity features of intensive care unit services and the clinical situation of patients themselves render correct prognosis fundamentally important not only for patients, their families and physicians, but also for hospital administrators, fund-providers and controllers. Prognostic indices have been developed for estimating hospital mortality rates for patients hospitalised in intensive care units, based on demographic, physiological and clinical data.

The most frequently used indices are **APACHE II** (Acute Physiology and Chronic Health Evaluation II), **APACHE III** (Acute Physiology And Chronic Health Evaluation III), **SAPS II** (Simplified Acute Physiology Score II) and MPM II (Mortality Probability Model II).[32,33]

SAPS II Score

Parameter	Value (score)						
HR			<40 (11)	40-69 (2)	70-119 (0)	120-159 (4)	>160 (7)
SBP			<70 (13)	70-99 (5)	100-199 (0)	>200 (2)	
Temp					<39°C (0)	>39°C (3)	
PaO_2/FIO_2	<100 (11)	100-199 (9)	>200 (6)				
UO (ml)		<500 (11)	>500 (4)		>1000 (0)		
S. Urea					<28 (0)	28-83 (6)	>84 (10)
TLC (10^3/cc)				<1 (12)	1-20 (0)	>20 (3)	
K				<3 (3)	3-4.9 (0)	>5 (3)	
Na				<125 (5)	125-144 (0)	>145 (1)	
Bicarb			<15 (6)	15-19 (3)	>20 (0)		
Bil					<4 (0)	4-5.9 (4)	>6 (9)
GCS	<6 (26)	6-8 (13)	9-10 (7)	11-13 (5)	14-15 (0)		

Age -score
<40 → 0
40-59 → 7
60-69 → 12
70-74 → 15
75-79 → 16
≥80 → 18

Chronic disease:
Metastatic cancer → 9
Hemat.malig → 10
AIDS → 17

Type of admission:
Sched. Surgical → 0
Medical → 6
Emer.surgical → 8

JAMA 1993;270(24):2957-2963

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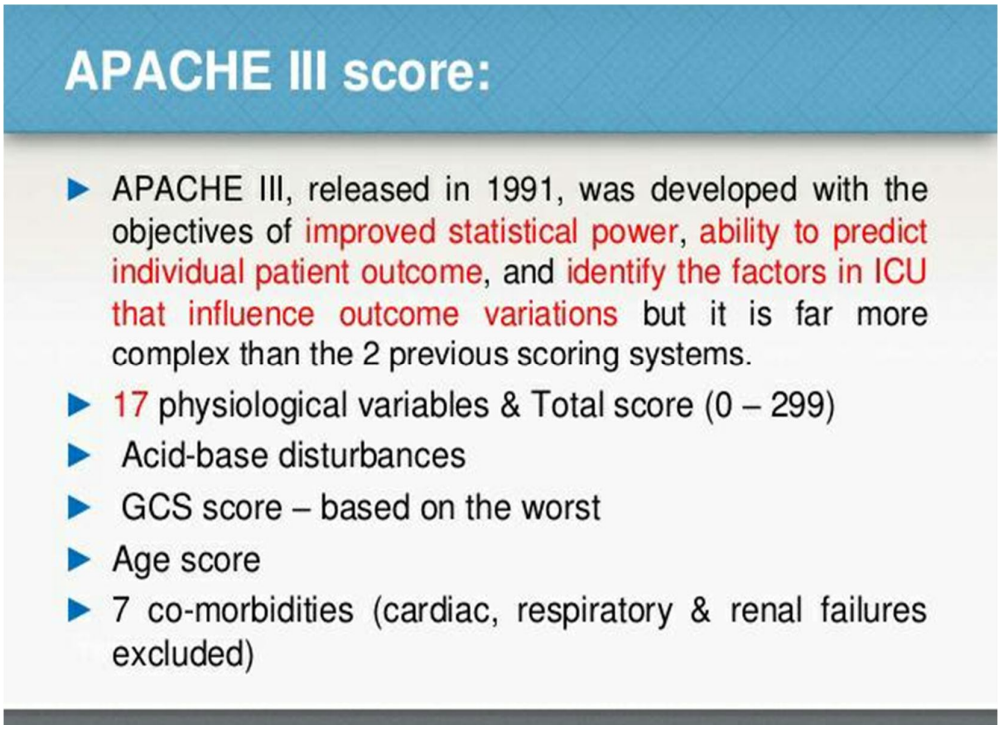
Apache II Scoring

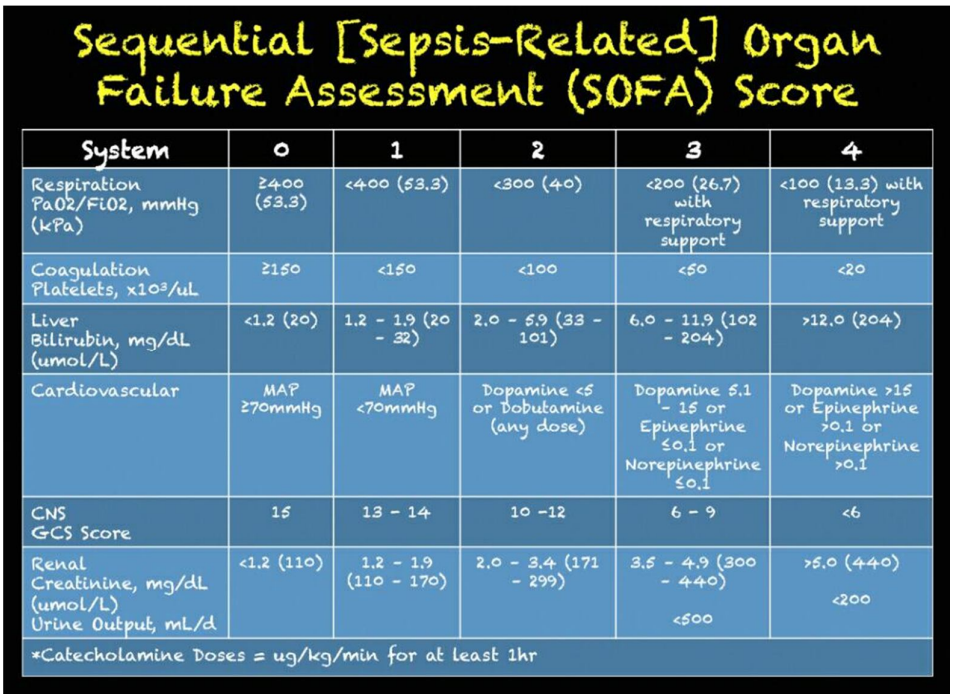
Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO2 **or** PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

The APACHE II index consists of a score that takes account of the patient's age, chronic health condition and physiological variables (internal temperature, heart rate, respiratory rate, oxygenation, arterial pH, sodium, potassium, creatinine, hematocrit, white blood cells and Glasgow coma score).

Markgraf et al.[34] compared the predictive capabilities of APACHE II, APACHE and SAPS II and concluded that the three indices have good discriminating power and that APACHE II has the best calibration. For this reason, it scored the most accurate mortality prediction.



Over the past years many scoring models have been developed to describe the severity of illness of intensive care patients or to predict the outcome of intensive care. As an example, the first Sepsis-related Organ Failure Assessment score, later called the **Sequential Organ Failure Assessment (SOFA) score**, was introduced in 1994[35].



Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score

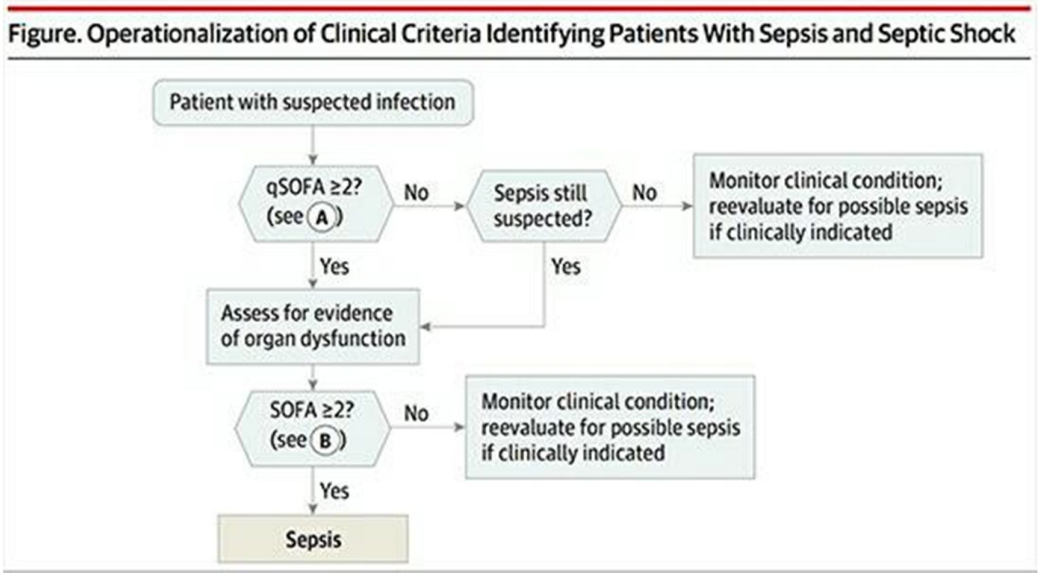
System	0	1	2	3	4
Respiration PaO2/FiO2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x10³/uL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (umol/L)	<1.2 (20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.9 (102 - 204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
CNS GCS Score	15	13 - 14	10 -12	6 - 9	<6
Renal Creatinine, mg/dL (umol/L) Urine Output, mL/d	<1.2 (110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440) <500	>5.0 (440) <200

*Catecholamine Doses = ug/kg/min for at least 1hr

The aim was to quantify the severity of the patients' illness based on the degree of organ dysfunction, serially over time. Although severity of illness scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Simplified Acute Physiology Score (SAPS)II[36] are based on the first 24 hrs of intensive care unit (ICU) admission, the SOFA scoring system takes into account the time course of a patient's condition during the entire ICU stay. This enables physicians to follow the evolving disease process.

The SOFA score is composed of scores from six organ systems, each graded from 0 to 4 points according to the degree of dysfunction. The assignment of scores for each organ system is based on one or more variables. For example, the SOFA score for renal function is derived from the serum creatinine level and urine output. Previous studies have shown that the SOFA score is suitable to evaluate organ dysfunction.

qSOFA	
RR > 22bpm sBP < 100mmHg Altered GCS	0 = Mortality < 1% 1 = Mortality 2-3% ≥2 = Mortality ≥10%
Screening for outcome rather than diagnosis	



Vincent et al. [35]stated that one of the criteria for a system that defines the degree of organ dysfunction is that it should be based on a limited number of simple but objective variables that are easily and routinely measured in every institution. With a total of 12 variables, the SOFA score contains fewer variables than most other ICU severity of illness scoring systems, such as APACHE II and SAPS II.

Materials & methods

MATERIALS AND METHODS

Study centre :

Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai – 3.

Study Design :

Single centre observational prospective study

Venue:

Rajiv Gandhi Government General Hospital, Chennai

Collaborating Departments :

- Institute of Biochemistry, MMC&RGGGH, Ch-3
- Institute of Pathology , MMC&RGGGH, Ch-3
- Barnard Institute of Radiology, MMC&RGGGH, Ch-3
- Institute of Microbiology, MMC&RGGGH, Ch-3

Duration :

Study was conducted from March 2017-August 2017

About fifty patients who attended our outpatient or emergency department with history of fever, cough with expectoration of recent onset, vomiting, burning micturition, breathlessness, confusion, or jaundice were selected randomly. A complete history was taken either from the patient or

his/ her attender including past history of jaundice, DM, hypertension, coronary artery disease, seizures, CVA, COPD, h/o prior surgery, malignancy, blood transfusion and retroviral status. His/her personal habits were enquired.

A complete physical examination was done with monitoring of vitals (temperature, pulse rate, respiratory rate and blood pressure) everyday or frequently as the patient condition demanded. A battery of blood investigations were done including renal functions, liver functions test, Complete blood count, HBs Ag, HIV, Widal test, MSAT, QBC for MP, blood –culture and sensitivity, serum CRP, prothrombin time and Arterial Blood gas analysis. Other investigations included were Urine analysis, urine – C/S, ECG, Chest X ray, USG abdomen and if required CT-Chest and CT-Abdomen.

CBC, RFT and LFT were repeated on the third day (48-72 hrs) and APACHE-II score and SOFA score were computed on first and third day.

C-reactive protein in serum was measured **by Immunoturbidimetric Assay** using clinical chemistry analysers.

Inclusion Criteria:

Patients older than 18yrs of age admitted in medical ward with criteria for sepsis ,i.e.,

Two or more of the following conditions:

1. fever (oral temperature >38°C) or hypothermia (<36°C);
2. tachypnea (>24 breaths/min);
3. tachycardia (heart rate >90 beats/min);
4. leukocytosis (>12,000/ L),
5. Leukopenia (<4,000/L), or >10% bands; plus proven or suspected microbial etiology

Exclusion Criteria :

1. Patients less than 18 years of age
2. Patients with rheumatic heart disease and collagen vascular disease
3. Patients with malignancy
4. Pregnant women
5. Patients on hormone replacement therapy
6. Patients who received antibiotics in prior 7 days

Statistical Analysis Plan :

Data analysed using statistical package - SPSS Software

Consent

All participants / attenders gave written informed consent.

Ethical Committee Approval

Institutional Ethics Committee of Madras Medical College approved the study.

Observations & results

OBSERVATION AND RESULTS

In the study of fifty cases of sepsis admitted in Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai, the following observations were made in sex incidence, age, Erythrocyte Sedimentation Rate, serum C-reactive protein level, APACHE II score within 24hours of admission and after 48-72 hrs, SOFA score within 24hours of admission and after 48-72 hrs and prognosis of the illness as follows:

Total number of patients	:	50
Total number of males	:	27 (54%)
Total number of females	:	23 (46%)

AGE INCIDENCE:

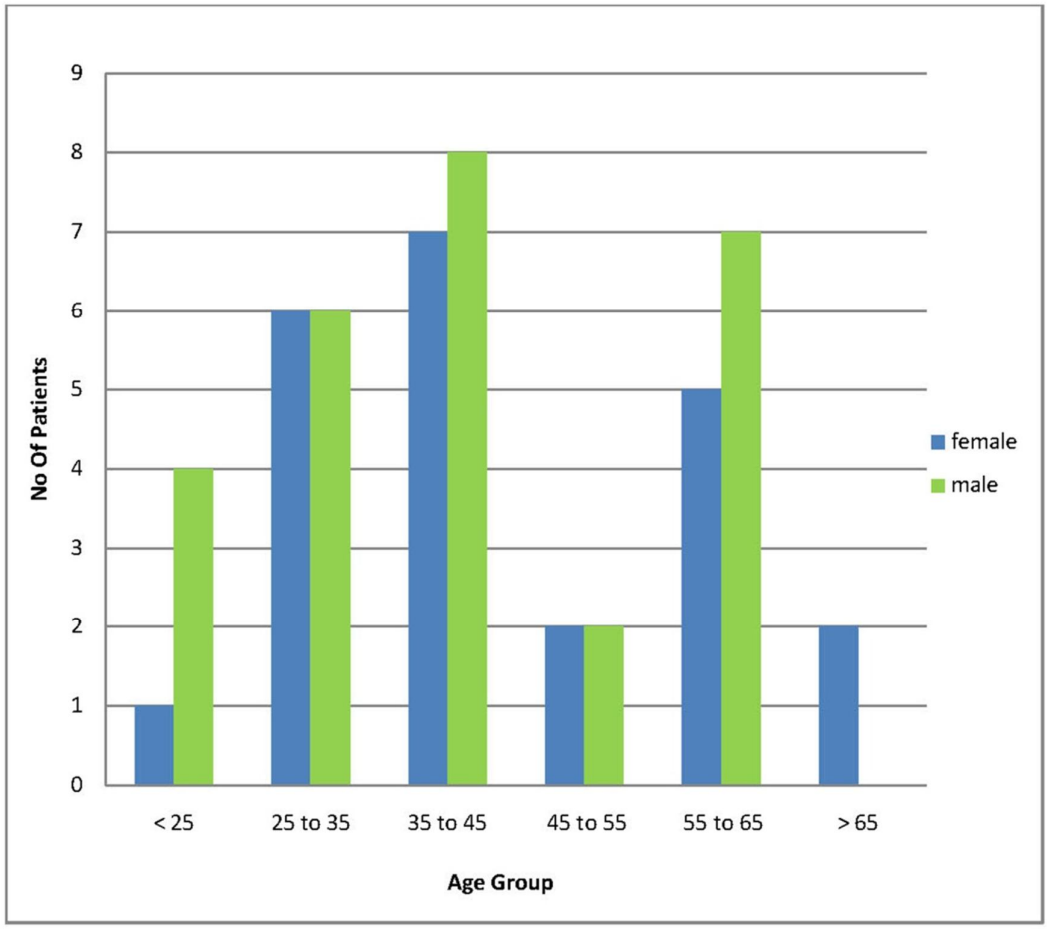
Age	Female	Male	Grand Total	Percentage
< 25	1	4	5	10%
25 to 35	6	6	12	24%
35 to 45	7	8	15	30%
45 to 55	2	2	4	8%
55 to 65	5	7	12	24%
> 65	2	0	2	4%
Grand Total	23	27	50	

Age average = 43.52

Age median = 42.5

Age mode = 45

Age Wise Distribution



Mortality: Overall

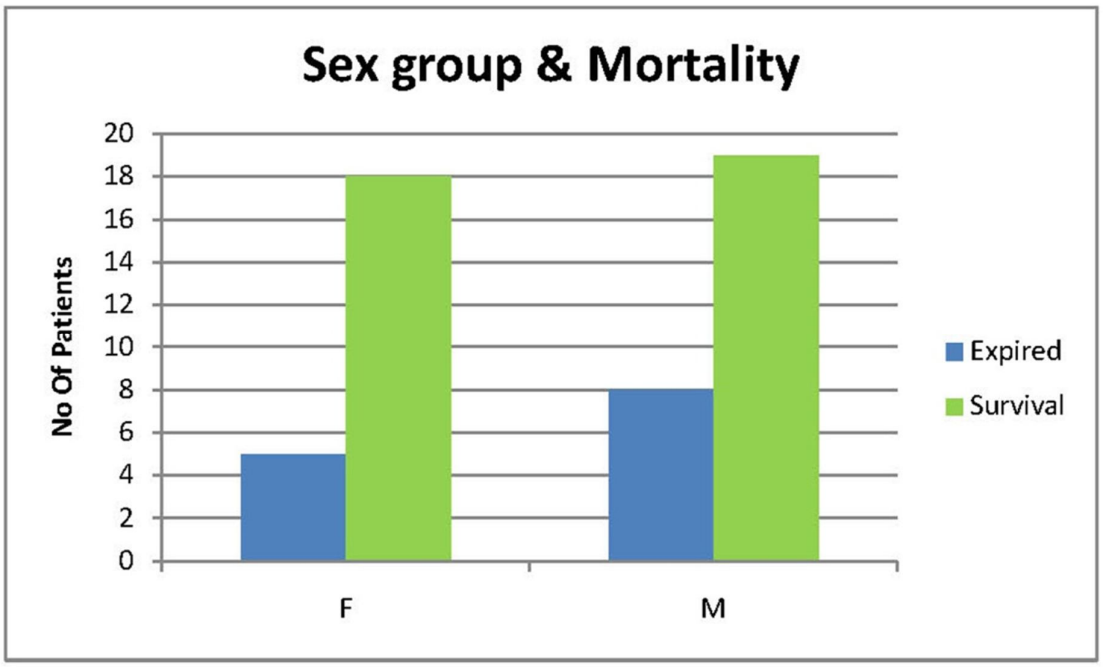
Total number of patients	:	50
Total number – survived	:	37
Total number – expired	:	13
Mortality percentage	:	26%

Females

Total number of females	:	23
Total number – survived	:	18
Total number – expired	:	5
Mortality percentage	:	21.7%

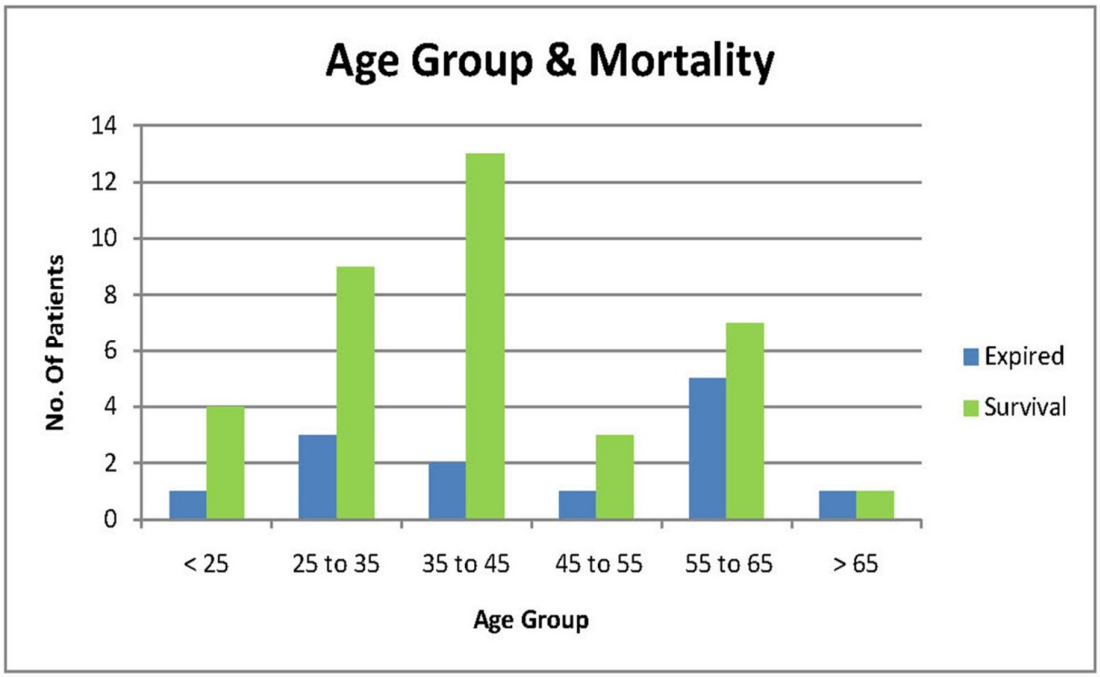
Males

Total number of males	:	27
Total number – survived	:	19
Total number – expired	:	8
Mortality percentage	:	29.5%



Age wise Mortality:

Age in yrs	Expired	Survival	Grand Total	Percentage
< 25	1	4	5	20%
25 to 35	3	9	12	25%
35 to 45	2	13	15	13.3%
45 to 55	1	3	4	25%
55 to 65	5	7	12	41.6%
> 65	1	1	2	50%
Grand Total	13	37	50	26%

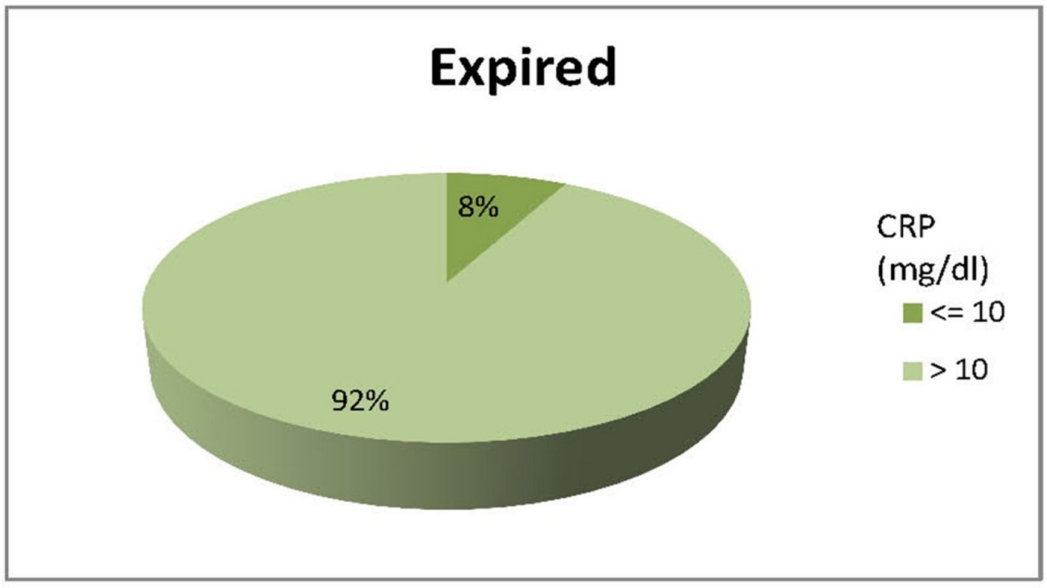


Serum CRP and Mortality :

Serum C-reactive protein and ESR were done on admission and APACHE II and SOFA score were computed on day 1 (within 24 hrs) and day 3 (48-72 hrs). out of the 50 patients, 10 patients had CRP level <=10mg/dl and 40 patien ts had CRP level >10mg/dl.

CRP AND MORTALITY

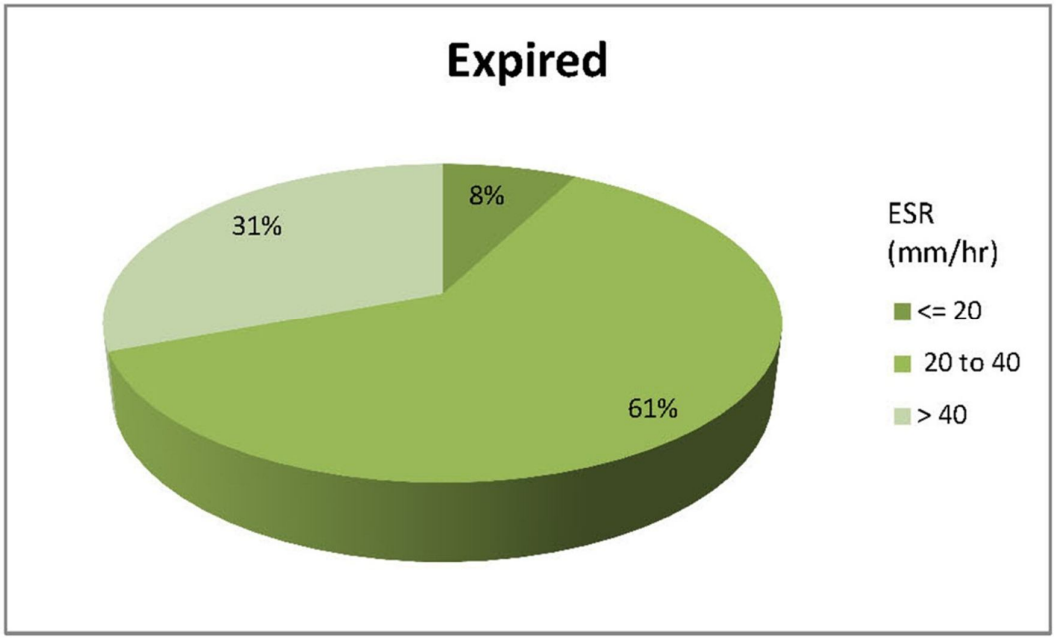
CRP (mg/dl)	Expired	Survival	Grand Total	Percentage
<= 10	1	9	10	10 %
>10	12	28	40	30 %
Grand Total	13	37	50	26 %



Of the 13 death patients, only one had CRP < 10mg/dl while all others had CRP > 10mg/dl.

ESR AND MORTALITY :

ESR (mm/hr)	Expired	Survival	Grand Total	Percentage
<= 20	1	12	13	7.69%
20 to 40	8	21	29	27.59%
> 40	4	4	8	50%
Grand total	13	37	50	26%



Of the 13 death patients, one had ESR <= 20mm/hr, eight had ESR between 20 and 40 mm/hr and four ha d ESR > 40mm/hr.

Serum CRP and Prognosis:

Before going into the analysis of serum CRP and ESR with prognosis, first we will look into the correlation between CRP and ESR and smoking, alcohol, hypertension and diabetes mellitus.

CRP vs Smoking

Smoking			
CRP (mg/dl)	**Yes**	**No**	**Grand Total**
<= 10	1	9	10
>10	8	32	40
Grand Total	9	41	50

p=0.66 NOT SIGNIFICANT

The correlation between smoking and CRP levels was not statistically significant.

CRP vs Alcohol

Alcohol			
CRP (mg/dl)	**Yes**	**No**	**Grand Total**
<= 10	1	9	10
>10	7	33	40
Grand Total	8	42	50

p=0.08 NOT SIGNIFICANT

The correlation between alcohol and CRP levels was not statistically Significant

CRP vs Hypertension

Hypertension			
CRP (mg/dl)	Yes	No	Grand Total
<= 10	0	10	10
>10	3	37	40
Grand Total	3	47	50

p=0.45 NOT SIGNIFICANT

The correlation between hypertension and CRP levels was not statistically significant.

CRP vs Diabetes mellitus

Diabetes mellitus			
CRP (mg/dl)	**Yes**	**No**	**Grand Total**
<= 10	3	7	10
>10	14	26	40
Grand Total	17	33	50

p=0.99 NOT SIGNIFICANT

The correlation between Diabetes mellitus and CRP levels was not statistically significant.

ESR vs Smoking

Smoking			
ESR (mm/hr)	**Yes**	**No**	**Grand Total**
<= 20	1	12	13
20 to 40	7	22	29
> 40	1	7	8
Grand Total	9	41	50

P = 0.41 NOT SIGNIFICANT

The correlation between smoking and ESR values was not statistically significant.

ESR vs Alcohol

Alcohol			
ESR (mm/hr)	**Yes**	**No**	**Grand Total**
<= 20	1	12	13
20 to 40	6	23	29
> 40	1	7	8
Grand Total	8	42	50

P = 0.61 NOT SIGNIFICANT

The correlation between alcohol and ESR values was not statistically significant.

ESR vs Diabetes mellitus

Diabetes mellitus			
ESR (mm/hr)	**Yes**	**No**	**Grand Total**
<= 20	3	10	13
20 to 40	12	17	29
> 40	2	6	8
Grand Total	17	33	50

P = 0.45 NOT SIGNIFICANT

The correlation between Diabetes mellitus and ESR values was not statistically significant.

ESR vs Hypertension

Hypertension			
ESR (mm/hr)	**Yes**	**No**	**Grand Total**
<= 20	0	13	13
20 to 40	3	26	29
> 40	0	8	8
Grand Total	3	47	50

P = 0.34 NOT SIGNIFICANT

The correlation between hypertension and ESR values was not statistically significant.

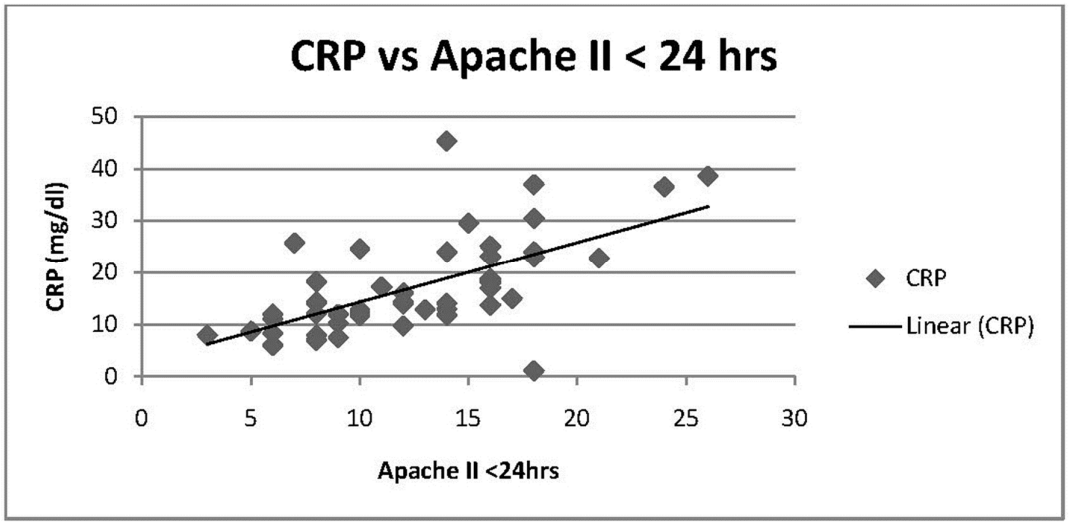
Comparison of sr CRP and prognosis :

Serum CRP on admission was compared with APACHE II score on admission and after 48 hours and also with SOFA score on admission and after 48 hours . The details are given below:

CRP vs Apache II < 24 hrs

Apache II<24 hrs			
CRP (mg/dl)	**<=10**	**> 10**	**Grand Total**
<= 10	8	2	10
> 10	14	26	40
Grand Total	22	28	50

P = 0.01 SIGNIFICANT

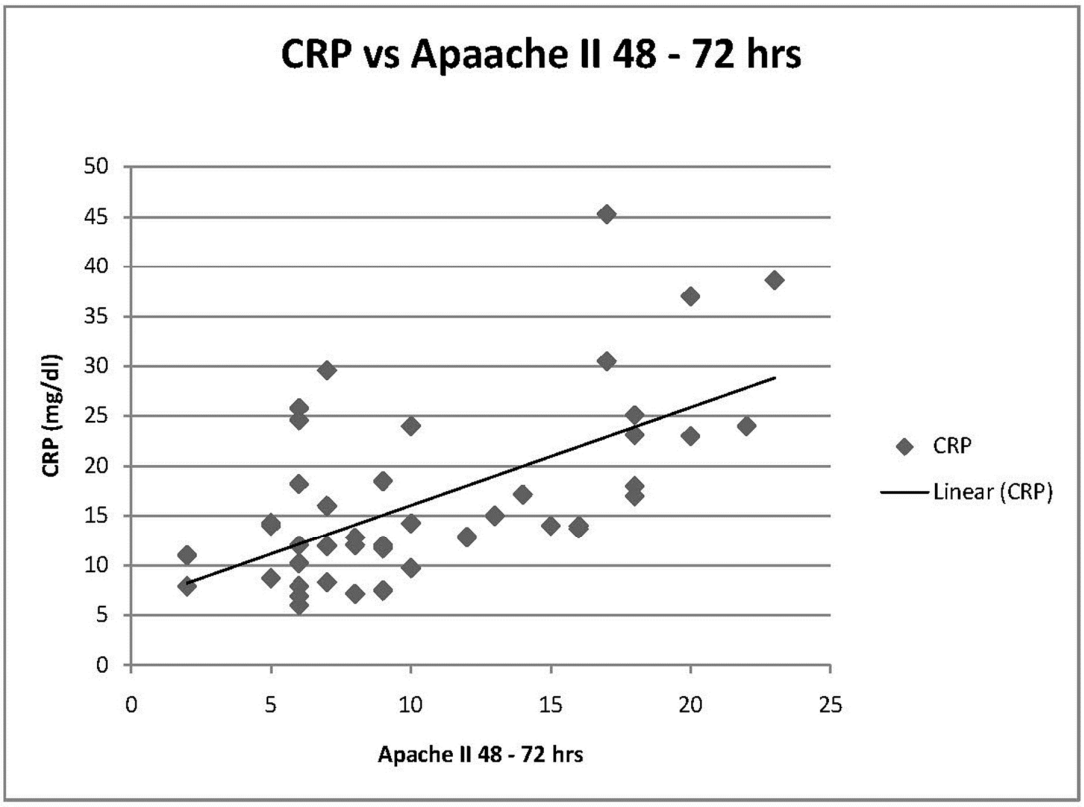


Correlation coefficient = 0.63

CRP vs Apaache II 48 - 72 hrs

Apache II 48-72hrs			
CRP (mg/dl)	**<=10**	**> 10**	**Grand Total**
<= 10	9	1	10
> 10	20	20	40
Grand Total	29	21	50

P = 0.01 SIGNIFICANT

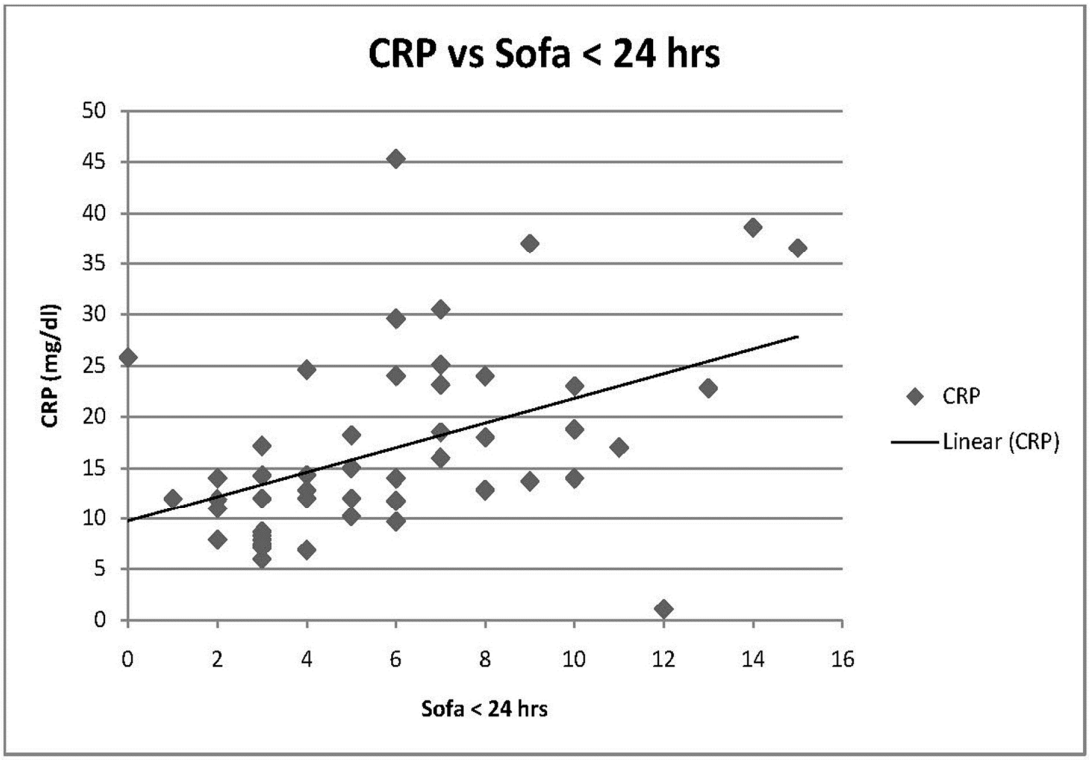


Correlation coefficient = 0.61

CRP vs Sofa < 24 hrs

SOFA < 24hrs			
CRP (mg/dl)	**<=7**	**>7**	**Grand Total**
<= 10	9	1	10
> 10	27	13	40
Grand Total	36	14	50

P = 0.07 NOT SIGNIFICANT

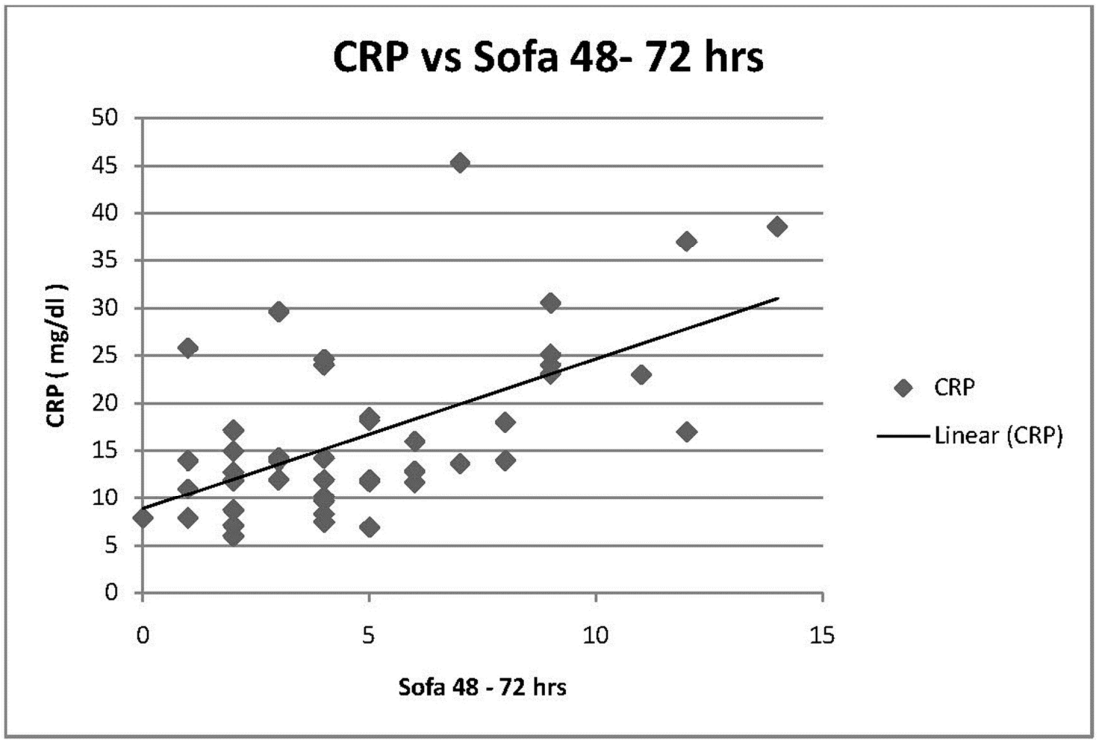


Correlation coefficient = 0.45

CRP vs Sofa 48- 72 hrs

SOFA 48-72hrs			
CRP (mg/dl)	**<=7**	**>7**	**Grand Total**
<= 10	9	1	10
> 10	27	13	40
Grand Total	36	14	50

P = 0.07 NOT SIGNIFICANT

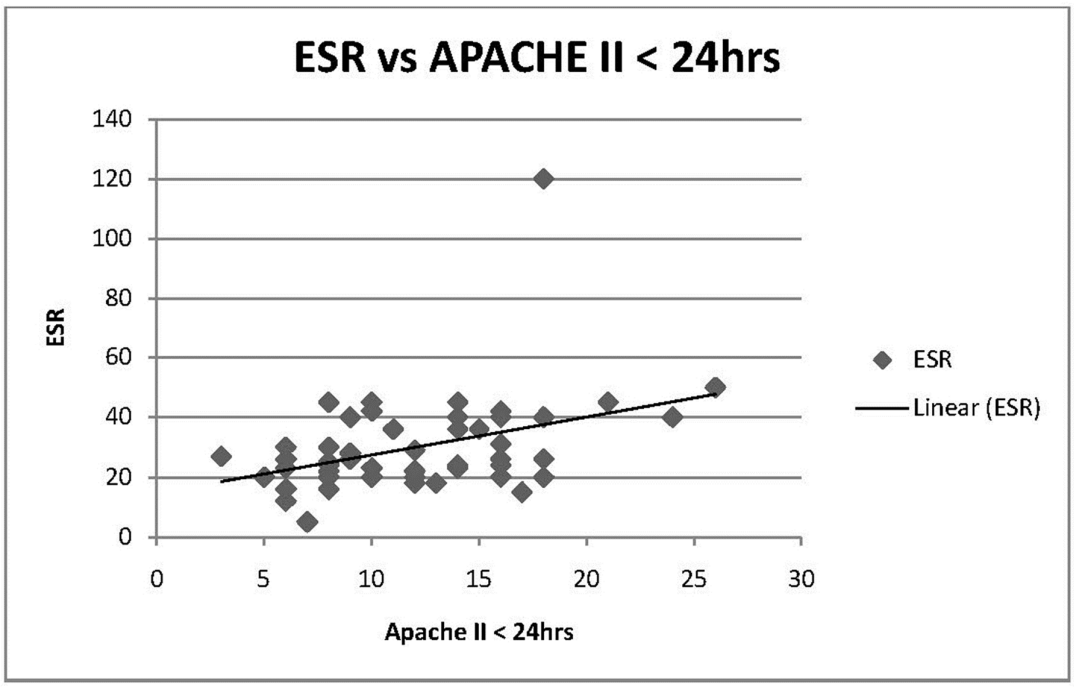


Correlation coefficient = 0.59

ESR vs APACHE II < 24hrs

Apache II<24 hrs			
ESR (mm/hr)	**<=10**	**> 10**	**Grand Total**
<= 20	7	6	13
20 to 40	12	17	29
> 40	3	5	8
Grand Total	22	28	50

P = 0.07 NOT SIGNIFICANT

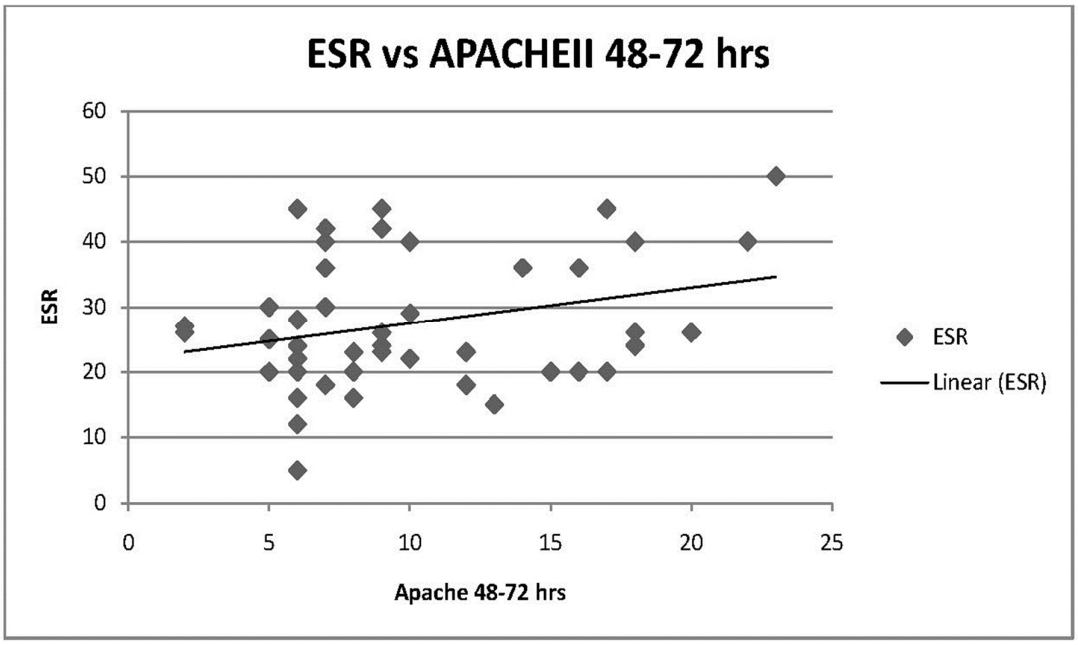


Correlation coefficient = 0.39

ESR vs APACHE II 48-72 hrs

Apache 48-72 hrs			
ESR (mm/hr)	**<=10**	**> 10**	**Grand Total**
<= 20	8	5	13
20 to 40	17	12	29
> 40	4	4	8
Grand Total	29	21	50

P = 0.99 NOT SIGNIFICANT

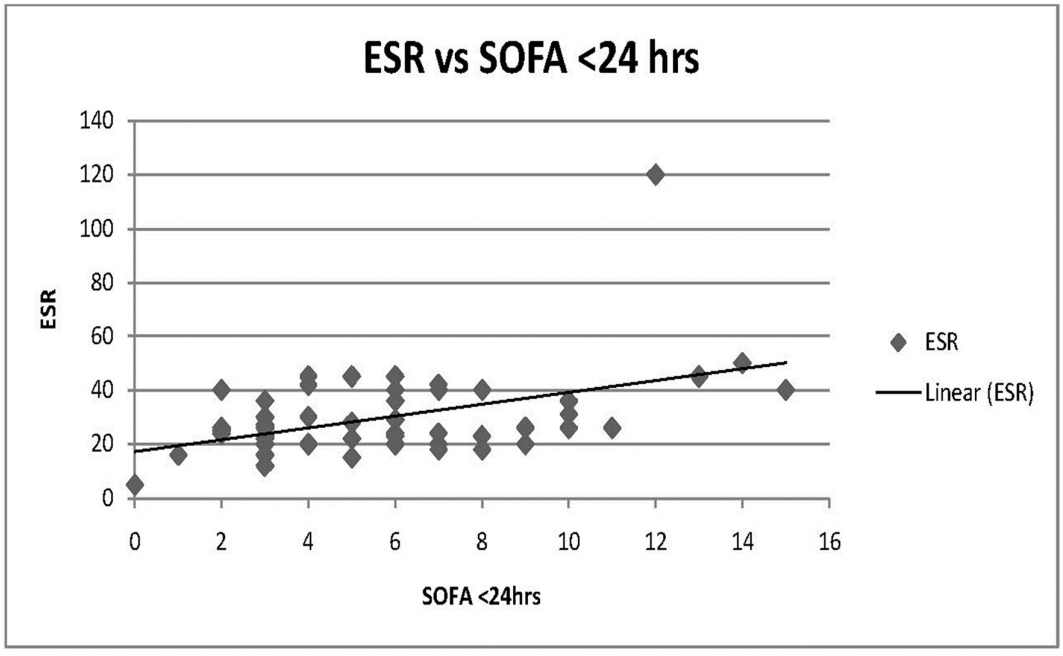


Correlation coefficient = 0.29

ESR vs SOFA <24 hrs

SOFA <24 hrs			
ESR (mm/hr)	**<=7**	**> 7**	**Grand Total**
<= 20	11	2	13
20 to 40	20	9	29
> 40	5	3	8
Grand Total	36	14	50

P = 0.48 NOT SIGNIFICANT

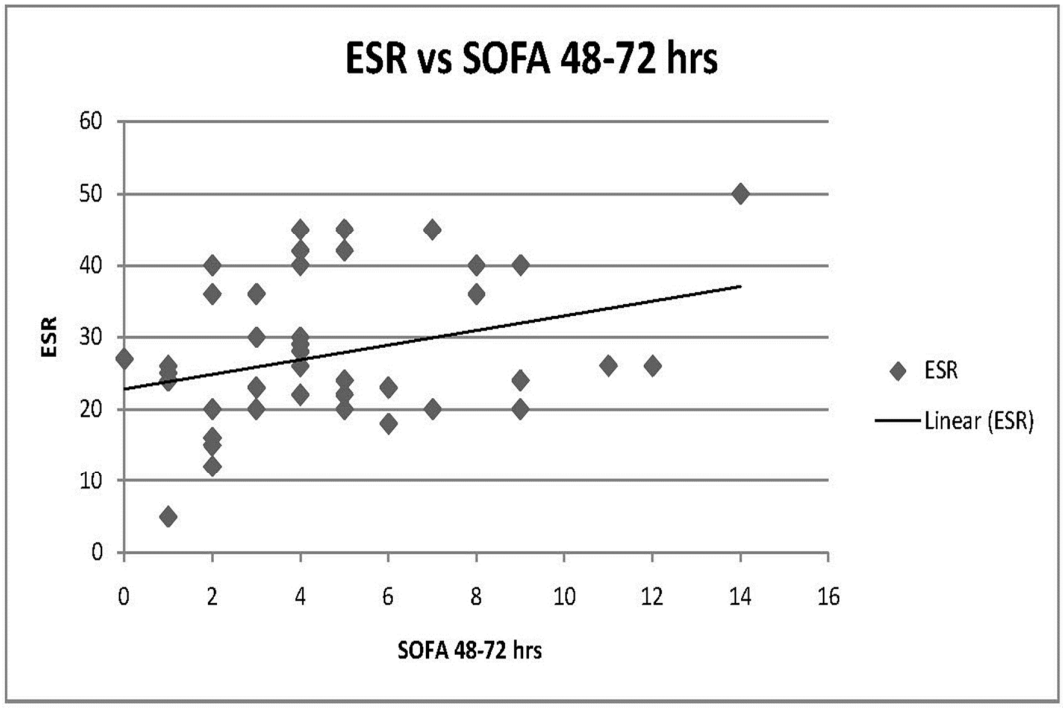


Correlation coefficient = 0.45

ESR vs SOFA 48-72 hrs

SOFA 48 - 72hrs			
ESR (mm/hr)	**<=7**	**> 7**	**Grand Total**
<= 20	12	1	13
20 to 40	19	10	29
> 40	5	3	8
Grand Total	36	14	50

P = 0.42 NOT SIGNIFICANT



Correlation coefficient = 0.33

	APACHE II <24HRS	APACHE II 48-72 HRS	SOFA <24HRS	SOFA 48-72 HRS
ESR (mm/hr)	P =0.07	P =0.99	P =0.48	P =0.42
	CC =0.39	CC =0.29	CC =0.45	CC =0.33
CRP (mg/dl)	P =0.01	P =0.01	P =0.07	P =0.07
	CC =0.63	CC =0.61	CC =0.45	CC =0.59

CC = Correlation coefficient

Sensitivity, Specificity and Positive Predictive Value Estimation for sr CRP:

CRP (mg/dl)	ApacheII <24 hrs >10	ApacheII <24 hrs <=10	Grand Total
> 10	26	14	40
<= 10	2	8	10
Grand Total	28	22	50

Sensitivity = TP/(TP + FN) * 100

= 26/28 * 100

= 92.85%

Specificity = TN/(TN+FP) * 100

= 36.36%

PPV = TP/(TP+FP) * 100

= 65%

NPV = TN/ (TN+ FN)* 100

= 80%

Discussion

DISCUSSION

The attention of the clinician must be directed towards the early diagnosis of infection[4]. However, bacteriological confirmation may be difficult to obtain and negative cultures do not exclude the presence of infection. In addition, manifestations of sepsis such as fever, leukocytosis and tachycardia are neither specific nor sensitive for infection, nor for monitoring the response to therapy [5].

Increasing understanding of the various inflammatory cascade mechanisms has given new insights and provided several markers that, in conjunction with other manifestations of sepsis, can be useful as indicators of infection.

C-reactive protein (CRP) is one such marker.

CRP is a marker of inflammation that has been used to monitor the course of infection and inflammatory diseases. Recently, CRP has been seen not only as a biochemical marker of inflammation but also as an active modulator of the inflammatory response. In this context, we evaluated ***the correlation of CRP levels with organ failure and mortality*** early after admission in a heterogeneous group of patients. We found that increased CRP concentrations were associated with organ failure, prolonged intensive

care and high infection and mortality rates. CRP concentrations > 10 mg/dL on admission were associated with a particularly high mortality.

C-reactive protein belongs to the pentraxin family of proteins, so called because they form a cyclic pentamer composed of five identical non-glycosylated sub-units. C-reactive protein binds to several polysaccharides and peptido-polysaccharides present in bacteria, fungi and parasites in the presence of calcium. These complexes activate the classical complement pathway, acting as opsonins and promoting phagocytosis[10].

Together with complement components, CRP is the only acute phase protein directly involved in the clearance of micro-organisms. The serum concentration of CRP in the normal human population has a median of 0.8 mg/l (interquartile range 0.3–1.7 mg/l) and is below 10 mg/l in 99% of normal samples[11,12]. Levels above these values are abnormal and indicate the presence of a disease process.

CRP is predominantly synthesised by the liver, mainly in response to interleukin 6 (IL-6). A good correlation exists between CRP and IL-6 levels[13]. Tumour necrosis factorα (TNFα) and IL-1 are also regulatory mediators of CRP synthesis. The secretion of CRP begins within 4–6 h of the stimulus, doubling every 8 h and peaking at 36–50 h.

Both acute systemic Gram-positive and Gram-negative bacterial infections, as well as systemic fungal infections cause marked CRP rises, even in immunodeficient patients. By contrast, CRP concentrations tend to be lower in most acute viral infections. Nevertheless, this rule is not absolute and uncomplicated infections with adenovirus, measles, mumps and influenza are sometimes associated with high CRP levels.

Evaluating changes in variables over time may be very helpful to assess the effects of interventions, as has been shown for organ dysfunction scoring systems. ***Lopes Ferreira et al***[28] reported that an increase in SOFA score during the first 48 hours in the ICU predicts a mortality rate of at least 50%, while a decreasing SOFA score is associated with a decrease in mortality rates from 50 to 27%. In patients with sepsis***, Presterl et al***[29] demonstrated a correlation between the plasma levels of CRP, IL-6 and tumor necrosis factor-sR, and the APACHE III and mortality probability model II scores. Both scoring systems, as well as CRP levels, were significantly higher in the nonsurvivors compared with the survivors. Nonsurvivors had significantly higher CRP levels from day 3 onwards. Our findings on the relation between the concentrations of CRP and APACHE II and SOFA scores indicate that both these parameters are useful indicators of severity and prognosis.

Bonig et al[30] reported that CRP levels > 10 mg/dL were predictive of poor outcome after hematopoietic stem cell transplantation in children. Chronic inflammation plays a role in the pathogenesis of cardiovascular diseases and elevated serum levels of CRP are associated with an increased risk of myocardial infarction and sudden cardiac death in apparently healthy subjects.

Zim, mermann et al [31] reported that high CRP levels in hemodialysis patients were closely related to high levels of vascular atherogenic risk factors and cardiovascular deaths. Serum concentrations of CRP and IL-6 have been shown to be inversely related to renal function in the predialytic phase of renal failure. In the present study, high CRP levels at admission were associated with more days of receiving extracorporeal support.

In our study, the overall mortality was 26% .The mortality rate in males was 29.5% and in females was 21.7%. The mortality rate increased with increasing age and it was 41.6% in patients with age group 55-65 years and 50% in patients with age >65 years of age.

Comparison of Age, CRP, Apache II and Sofa scores between expired and survived patients

	Expired	Survived
No of patients	13	37
Age	47.07	42.27
CRP	25.98 + 11.64	13.77 + 5.64*
Apache II <24 hrs	18.38 + 3.4	10.16 + 3.59*
Sofa <24 hrs	10 + 2.86	4.54 + 2.28*

*P <0.05 (T test)

The mortality rate in patients with serum CRP > 10 mg/dl was 30% while the mortality rate in patients with serum CRP < 10 mg/dl was 10%. The patients with serum CRP > 10 mg/dl also had prolonged hospital stay and multiple organ dysfunctions.

In our study, the number of patients with serum CRP < 10 mg/dl was 10 and with serum CRP > 10 mg/dl was 40.

In the srCRP < 10 mg/dl group, the mean Apache II score on admission was 8.3 and after 48 hours was 6.55. The mean SOFA score on admission was 4.3 and after 48 hours was 3. In the srCRP > 10 mg/dl

group, the mean Apache II score on admission was 13.3 and after 48 hours was 11.64. The mean SOFA score on admission was 6.4 and after 48 hours was 5.57.This is consistent with other studies which used serum CRP as a prognostic marker in sepsis such as *Lopez et al,2011* [37] Castelli *et al ,2004*[38] *Loboet al,2003* [3]

[9]**Comparison of Age, Apache II and Sofa scores between the two CRP groups**

	CRP ≤10 mg/dl	**CRP >10 mg/dl**
No of patients	10	40
Age	42.5	43.775
Apache II <24 hrs	8.3 + 3.34	13.3 + 4.79*
Apache II 48-72 hrs	6.55 + 2.35	11.64 + 5.86*
Sofa <24 hrs	4.2 + 2.94	6.4 + 3.52
Sofa 48-72 hrs	3 + 1.66	5.57 + 3.39*

*P <0.05 (T test)

Limitations

LIMITATIONS OF STUDY

1. We found that in our study there were some limitations with the sample size which precluded us from getting statistical significance with regard to certain variables with the severity of sepsis.
2. In our study, serum CRP were measured at the time of presentation and were not measured serially due to financial constraints and hence could not follow its evolution over the duration of hospital stay. Changes are very helpful in diagnosis as well as in monitoring response to therapy, as CRP levels are only determined by the rate of synthesis.

Conclusion

CONCLUSION

1. Determination of CRP is an economical, consistent and reproducible test and is available in almost every hospital.
2. Serum CRP has been found to be significantly elevated with increasing severity of SEPSIS which could lead to increased predisposition to morbidity and mortality.
3. ESR is not a good prognostic marker for sepsis
4. Mortality of sepsis increases with the age of the patient.
5. Serum CRP levels correlated well with the Apache II score on admission and after 48 hours, but had poor correlation with SOFA score.
6. Serum ESR levels did not correlate with the Apache II score and SOFA score, both on admission and after 48 hours.

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Annexures

SERUM LACTATE DEHYDROGENASE AND C REACTIVE PROTEIN LEVEL IN SEPSIS AND ITS CORRELATION WITH APACHE-II SCORE

PROFORMA

S. No.

Name : Age: Sex:

Occupation:

Contact No.:

Hospital No.:

Symptoms:

- Fever
- Cough with expectoration
- Jaundice
- Vomiting
- Breathlessness
- Burning micturation
- Seizures
- Altered sensorium
- Bleeding tendencies

PAST HISTORY

- Jaundice
- Surgery
- Blood transfusion

- Diabetes mellitus
- Hypertension
- Chronic liver disease
- Malignancy
- Retroviral status

v) PERSONAL HISTORY

- Alcohol
- Smoking
- Drug abuse
- Marital Status
- Promiscuity

EXAMINATION

Signs:

Consciousness : Orientation :

Clubbing :

Pallor : Y/ N Cyanosis :

Jaundice : Y / N Pedal edema :

Lymphadenopathy : JVP :

Skin – petechia or purpura : Y / N

Vital signs :

Temperature :

Respiratory rate:

Pulse :

Blood pressure:

Systemic examination :

CVS :

RESPIRATORY SYSTEM:

ABDOMEN :

CNS:

GCS:
Neck stiffness: Y/N

INVESTIGATIONS
1. Complete Hemogram

Hb%	Platelets
TC	ESR
DC	Hematocrit

2. Urine analysis

3. Blood sugar

4 Serum creatinine Blood urea
Urine output
5. Serum Na Serum K
6. Liver function tests

T. Bilirubin :	SAP :
D. Bilirubin :	T. Protein :
ID. Bilirubin :	Albumin :
AST :	
ALT :	

7. PT / INR :
8. ECG
9. X- ray chest
10.Blood C/S
11.Urine C/S (if necessary)
12. Sputum C/S
13. MSAT WIDAL QBC for MP
14. Ultrasound abdomen
15. CT Chest if necessary
16. Arterial blood gas analysis
17. PaO2

18. CRP level LDH level

19. HbsAg AntiHCV antibodies

Day 0	Day2

ACUTE PHYSIOLOGY SCORE									
Score	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**
Rectal temperature, °C	≥41	39.0–40.9		38.5–38.9	36.0–38.4	34.0–35.9	32.0–33.9	30.0–31.9	≤29.9
Mean blood pressure, mmHg	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate	≥50	35–49		25–34	12–24	10–11	6–9		≤5
Arterial pH	≥7.70	7.60–7.69		7.50–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
Oxygenation									
If $FI_{O_2} > 0.5$, use $(A - a) D_{O_2}$	≥500	350–499	200–349		<200				
If $FI_{O_2} \leq 0.5$, use Pa_{O_2}					>70	61–70		55–60	<55
Serum sodium, meq/L	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
Serum potassium, meq/L	≥7.0	6.0–6.9		5.5–5.9	3.5–5.4	3.0–3.4	2.5–2.9		<2.5
Serum creatinine, mg/dL	≥3.5	2.0–3.4	1.5–1.9		0.6–1.4		<0.6		
Hematocrit	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
WBC count, 10^3/mL	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1

GLASGOW COMA SCORE[b,c]			
Eye Opening	**Verbal (Nonintubated)**	**Verbal (Intubated)**	**Motor Activity**
4—Spontaneous	5—Oriented and talks	5—Seems able to talk	6—Verbal command
3—Verbal stimuli	4—Disoriented and talks	3—Questionable ability to talk	5—Localizes to pain
2—Painful stimuli	3—Inappropriate words	1—Generally unresponsive	4—Withdraws to pain
1—No response	2—Incomprehensible sounds		3—Decorticate
	1—No response		2—Decerebrate
			1—No response

POINTS ASSIGNED TO AGE AND CHRONIC DISEASE AS PART OF THE APACHE II SCORE		
Age, Years	**Score**	
<45	0	
45–54	2	
55–64	3	
65–74	5	
≥75	6	

Chronic Health (History of Chronic Conditions)[d]	Score
None	0
If patient is admitted after elective surgery	2
If patient is admitted after emergency surgery or for reason other than after elective surgery	5

Sepsis-related organ failure assessment (SOFA) score.

Organ system	Measure
Respiration	PaO2 to FiO2 ratio
Coagulation	Platelet count
Liver	Serum bilirubin
Cardiovascular	Hypotension
Central nervous system	Glasgow coma score
Renal	Serum creatinine or urine output

Measure	Finding	Points	Day0	Day2
PaO2 to FiO2 ratio	>400 (mmHg)	0		
	300–399 (mmHg)	1		
	200–299 (mmHg)	2		
	100–199 (mmHg)	3		
	<100 (mmHg)	4		
Platelet count	1500/ml	0		
	1000–149 999/ml	1		
	500–99 999/ml	2		
	200–49 999/ml	3		
	<200 per ml	4		
Serum bilirubin	<1.2 mg/dl	0		
	1.2–1.9 mg/dl	1		
	2.0–5.9 mg/dl	2		
	6.0–11.9 mg/dl	3		
	12.0 mg/dl	4		
Hypotension	Mean arterial pressure _ 70 (mmHg)	0		
	Mean arterial pressure <70 then (no pressor agents used) (mmHg)	1		
	Dobutamine any dose	2		
	Dopamine _ 5 mg/kg per min	2		
	Dopamine >5–15 mg/kg per min	3		

	Dopamine >15 mg/kg per min	4
	Adrenaline _ 0.1 mg/kg per min	3
	Adrenaline >0.1 mg/kg per min	4
	Noradrenaline _ 0.1 mg/kg per min	3
	Noradrenaline >0.1 mg/kg per min	4
Glasgow coma score	15	0
	13–14	1
	10–12	2
	6–9	3
	3–5	4
Serum creatinine or urine output		
	Serum creatinine <1.2 mg/dl	0
	Serum creatinine 1.2–1.9 mg/dl	1
	Serum creatinine 2.0–3.4 mg/dl	2
	Serum creatinine 3.5–4.9 mg/dl	3
	Urine output 200–499 ml/day	3
	Serum creatinine >5.0 mg/dl	4
	Urine output <200 ml/day	4

PaO2 is in mmHg and FiO2 in per cent, from 0.21 to 1.00.
Adrenergic agents as administered for at least 1 hour with doses in mg/kg per min.
A score of 0 indicates normal and a score of 4 indicates most abnormal.
Data can be collected and the score calculated daily during the course of the admission.
Interpretation: minimum total score: 0; maximum total score: 24.
The higher the organ score, the greater the organ dysfunction.
The higher the total score, the greater the multiorgan dysfunction.

Mortality rate by SOFA score.

Organ system	0	1	2	3	4
Respiratory	20%	27%	32%	46%	64%
Cardiovascular	22%	32%	55%	55%	55%
Coagulation	35%	35%	35%	64%	64%
CNS	32%	34%	50%	53%	56%
Renal	25%	40%	46%	56%	64%

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

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CERTIFICATE OF APPROVAL

To
Dr.R.Prithiviraj
Post Graduate in M.D.(General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.R.Prithiviraj,

The Institutional Ethics Committee has considered your request and approved your study titled **"PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS USING C-REACTIVE PROTEIN & APACHE II SCORING SYSTEM " - NO.17022017**

The following members of Ethics Committee were present in the meeting hold on **07.02.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.S.Suresh, MS., Prof.of Surgery, MMC, Ch-3	: Member
5.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
6.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
7.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
8.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

URKUND

Urkund Analysis Result

Analysed Document: Prithivi thesis sepsis.docx (D30483353)
Submitted: 2017-09-11 15:47:00
Submitted By: drrprithivi90@gmail.com
Significance: 14 %

Sources included in the report:

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PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS USING C-REACTIVE PROTEIN AND APACHE II SCORING SYSTEM"** of the candidate **DR.R. PRITHIVIRAJ** with registration Number **201511023** for the award of **M.D** in the branch of **GENERAL MEDICINE**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **14 percentage** of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

INFORMATION SHEET

We are conducting a study on **"PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS USING C-REACTIVE PROTEIN & APACHE II SCORING SYSTEM."** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your co-operation to undergo relevant investigations as per need may be valuable to us.

The purpose of this study is to find the outcome of patients with sepsis by using both scoring system(APACHE II) and CRP values

We are selecting certain cases and if you are found eligible, we would like to perform extra tests and you will be subjected to a non invasive procedure like ultra sonogram,x-Ray chest which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator

Signature/left thumb impression of Participant

Date :

Place :

PATIENT CONSENT FORM

Study Detail : **" PREDICTION OF OUTCOME IN PATIENTS WITH SEPSIS USING C-REACTIVE PROTEIN & APACHE II SCORING SYSTEM"**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

In Patient Number :

Patient may check (√) these circles

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ○

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ○

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ○

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ○

e) I hereby consent to participate in this study. ○

f) I hereby give permission to undergo detailed clinical examination and relevant investigations as required. ○

Signature/thumb impression

Patient's Name and Address:

Signature of Investigator

Study Investigator's Name:

Dr.R.PRITHIVIRAJ

MASTER CHART

S. No.	Age	Sex	CRP (mg/dl)	ESR (mm/hr)	Plt.Count / mcl	PT (Seconds)	Apache (24 hrs)	AP (48-72)
1	55	M	10.2	28	80,000	14	9	6
2	42	M	25.8	5	1,56,000	12	7	6
3	21	M	1.1	120	1,14,000	42	18	*
4	65	M	17.16	36	2,18,000	20	11	14
5	26	M	7.9	27	68,000	15	3	2
6	35	F	11.92	40	70,000	23	9	7
7	40	M	29.58	36	1,96,000	20	15	7
8	30	M	11	26	2,32,000	13	6	2
9	28	M	18.5	42	1,72,000	15	16	9
10	34	M	38.6	50	1,40,000	18	26	23
11	27	F	18.78	31	1,60,000	14	16	*
12	36	M	36.58	40	1,20,000	13	24	*
13	29	F	8.7	20	1,90,000	26	5	5
14	28	M	45.3	45	2,56,000	16	14	17
15	45	F	14	25	1,80,000	16	8	5
16	30	F	24	40	1,67,000	19	14	10
17	53	M	37	26	1,10,000	23	18	20
18	58	F	24.6	45	2,10,000	19	10	6
19	63	F	14.3	30	1,30,000	15	8	5
20	26	F	18.2	22	87,000	21	8	6
21	46	F	23.12	40	1,45,000	26	16	18
22	63	M	7.9	24	1,90,000	17	8	6
23	60	F	22.8	45	1,70,000	22	21	*
24	24	M	12	23	1,45,000	14	6	8
25	65	M	30.5	20	3,09,000	20	18	17

Master Chart….2

S. No.	Sofa 24	Sofa 48-72	Smoking	Alcohol	Hyper tension	Diabetes	Diagnosis	Outcome
1	5	4	Y	Y	N	N	Rt LL pneumonia	Survival
2	0	1	N	N	N	N	UTI	Survival
3	12		N	N	N	N	ALF	Expired
4	3	2	N	Y	N	N	Rt UL pneumonia	Survival
5	3	0	Y	N	N	N	Pneumonia	Survival
6	2	2	N	N	N	N	UTI	Survival
7	6	3	Y	Y	N	N	Rt ML pneumonia	Survival
8	2	1	Y	Y	N	N	Lt LL pneumonia	Survival
9	7	5	N	N	N	N	B/L Bronchopneumonia	Survival
10	14	14	Y	Y	N	N	Lt LL pneumonia	Expired
11	10		N	N	N	N	B/L Bronchopneumonia	Expired
12	15		Y	Y	N	N	ARDS	Expired
13	3	2	N	N	N	N	B/L Bronchopneumonia	Survival
14	6	7	N	N	N	N	Lepto/ ARDS	Expired
15	2	1	N	N	N	Y	UTI	Survival
16	6	4	N	N	N	N	Rt LL pneumonia	Survival
17	9	12	N	N	Y	Y	Rt LL pneumonia	Expired
18	4	4	N	N	N	Y	Rt LL cellulitis	Survival
19	4	3	N	N	N	N	Lt UL pnemonia	Survival
20	5	5	N	N	N	N	UTI	Survival
21	7	9	N	N	N	Y	B/L Bronchopneumonia	Survival
22	2	1	N	N	N	N	Lt LL pneumonia	Survival
23	13		N	N	N	Y	B/L pneumonia	Expired
24	3	3	N	N	N	N	UTI	Survival
25	7	9	N	N	N	Y	Rt renal abscess	Expired

Master Chart….3

S. No.	Age	Sex	CRP (mg/dl)	ESR (mm/hr)	Plt.Count / mcl	PT (Seconds)	Apache (24 hrs)	AP (48-72)
26	43	F	12.8	20	2,30,000	16	10	8
27	45	M	16	18	1,80,000	19	12	7
28	34	M	6	12	70,000	16	6	6
29	63	M	18	40	1,90,000	28	16	18
30	38	M	12	16	2,87,000	19	6	6
31	62	M	14	20	1,85,000	14	12	15
32	67	F	23	26	2,20,000	22	18	20
33	56	F	8.3	30	1,30,000	14	6	7
34	35	F	7.12	16	1,98,000	16	8	8
35	48	F	12.9	23	3,45,000	26	14	12
36	25	M	11.8	24	2,10,000	20	14	9
37	45	F	17	26	2,15,000	20	16	18
38	65	M	13.7	20	2,30,000	23	16	16
39	43	M	15	15	3,68,000	12	17	13
40	24	M	14	36	1,45,000	15	14	16
41	56	M	24	40	56,000	24	18	22
42	38	F	14.26	22	80,000	14	12	10
43	72	F	9.7	29	68,000	32	12	10
44	38	F	11.7	23	3,90,000	16	10	9
45	42	M	12.8	18	2,30,000	21	13	12
46	45	M	7.45	26	4,80,000	14	9	9
47	57	F	25.1	24	1,10,000	17	16	18
48	24	F	12	42	2,00,000	22	10	7
49	44	F	6.9	20	3,12,000	18	8	6
50	38	F	12	45	2,38,000	26	8	9

Master Chart….4

S. No.	Sofa 24	Sofa 48-72	Smoking	Alcohol	Hyper tension	Diabetes	Diagnosis	Outcome
26	4	2	N	N	N	N	Rt LL pneumonia	Survival
27	7	6	N	N	N	N	UTI	Survival
28	3	2	N	Y	N	N	Rt UL pneumonia	Survival
29	8	8	Y	Y	N	Y	B/L pneumonia	Expired
30	1	2	Y	N	N	N	Lt LL pneumonia	Survival
31	6	3	N	N	N	Y	Lt UL pnemonia	Survival
32	10	11	N	N	Y	Y	Rt Psoas abscess	Expired
33	3	4	N	N	N	Y	UTI	Survival
34	3	2	N	N	N	N	Rt LL pneumonia	Survival
35	8	6	N	N	N	Y	Rt LL cellulitis	Survival
36	6	5	N	N	N	N	Rt LL pneumonia	Survival
37	11	12	N	N	Y	Y	Rt LL pneumonia	Expired
38	9	7	N	N	N	Y	Rt UL pneumonia	Survival
39	5	2	N	N	N	N	Rt UL pneumonia	Survival
40	10	8	N	N	N	N	Sepsis/ ARDS	Survival
41	8	9	Y	N	N	Y	B/L pneumonia	Expired
42	3	4	N	N	N	N	Rt ML pneumonia	Survival
43	6	4	N	N	N	Y	Rt pyelonephritis	Survival
44	6	6	N	N	N	N	UTI	Survival
45	8	6	N	N	N	N	Lt UL pnemonia	Survival
46	3	4	N	N	N	Y	Rt Psoas abscess	Survival
47	7	9	N	N	N	Y	Rt LL pneumonia	Expired
48	4	4	N	N	N	N	Rt LL pneumonia	Survival
49	4	5	N	N	N	N	UTI	Survival
50	5	5	N	N	N	N	Lt UL pnemonia	Survival